CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074374 /S001, S002

Trade Name : PRIMSOL SOLUTION 25MG(BASE)/5ML

Generic Name: Trimethoprim Hydrochloride Oral Solution 25mg(Base)/5ml

Sponsor : Ascent Pediatrics, Inc.

Approval Date: June 17, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074432 /S001, S002

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Final Printed Labeling	X			
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Chemistry Review(s)				
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074374 /S001, S002

APPROVAL LETTER

NDA 74-374/S-001, S-002

JUN 17 1997

Ascent Pediatrics, Inc.
Attention: Robert W. Mendes, Ph.D.
187 Ballardvale Street, Suite B125
Wilmington, MA 01887

Dear Sir:

This is in reference to your supplemental new drug application dated December 29, 1995, submitted pursuant to 21 CFR 314.70 regarding your new drug application for Primsol Solution (Trimethoprim Hydrochloride Oral Solution) 25 mg(base)/5 mL.

Reference is also made to your amendment dated April 2, 1997.

The supplemental application provides for the use of Primsol Solution to treat acute otitis media in pediatric patients.

We have completed the review of this supplemental application and it is approved. However, at the time of next printing, further revise your insert labeling as follows:

CLINICAL PHARMACOLOGY

1. Susceptibility Testing

   Revise subsection heading to read, Susceptibility Tests

2. Diffusion Techniques

   Revise the ultimate sentence of the second paragraph to read, ...following criteria.

Please note that these changes may be submitted in an annual report provided the changes are described in full.

We remind you that you must comply with the requirements for an approved new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

cc:
NDA 74-374/S-001
Division File
HFD-92/with labeling
HFD-600/Reading File
HFD-610/JPhillips
Field Copy
HFD-520/Div. Files
HFD-2/M. Lumpkin
HFD-520/Label File/B. Duvall-Miller
HFD-520/Div. Files
HFD-520/ActDivDir/D. Feigal
HFD-520/DepDir/L. Gavrilovich
HFD-520/CSO/B. Duvall-Miller
HFD-520/MO/S. Maloney
HFD-520/Micro/H. Silver
HFD-725/Stats/R. Harkins
HFD-520/SMO/J. Soreth
HFD-101/L. Carter
DISTRICT OFFICE
HFD-40/DDMAC

njg/5/13/97/X:\NEW\FIRMSAM\ASCENT\LTRS&REV\74374S01.APL
APPROVAL LETTER - SINGLE SUPPLEMENT

Endorsements:
HFD-613/LGolson/CHoppes/JGrace (no cc)
HFD-600/M. Fanning (no cc)
HFD-629/G. Schaefer/JBuccine (no cc)

EXCLUSIVITY SUMMARY for NDA # 74-374 SUPPL # S-002

Trade Name Primsol **Generic Name** Trimethoprim hydrochloride
Applicant Name Ascent Pediatrics, Inc. **HFD-520**

Approval Date June 17, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /__/ NO /✓/

   b) Is it an effectiveness supplement?

   YES /✓/ NO /__/

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

   d) Did the applicant request exclusivity?

   YES /✓/ NO /__/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 17-952 Trimpex

NDA # _____ _____

NDA # _____ _____

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if

known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /✓/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /✓/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # T-OM-02

Investigation #2, Study # T-OM-01

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /__/	NO /✓/
Investigation #2	YES /__/	NO /✓/
Investigation #3	YES /__/	NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # T-OM-02

Investigation #_, Study # T-OM-01

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ___ YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # ___ YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

_____ 6/23/97

Signature Date

Title: Project Manager

6/26/97

Signature of Division Director Date

cc: Original NDA 74-374
Division File
HFD-85/Mary Ann Holovac

Exclusivity

EXCLUSIVITY DETERMINATION CHECKLIST

ANDA # 74-374 SUPPL. # 001 APPLICANT ASCENT PEDIATRICS TR. NAME PRIMSOL SOLUTION

ACTIVE INGRED. TRIMETHOPRIM HCl POTENCY 25mg/5mL DOSAGE FORM/ROUTE ORAL SOLUTION

APPROVAL DATE _____

TYPE OF APPLICATION: FULL NDA ____ 505(b)(2) ___ EFFIC. SUPP. ___ OTHER (SPECIFY) X

EXCLUSIVITY REQUESTED: 5 YR ___ 3 YR X NONE ___ ANDA EFFIC. SUPP.

QUALIFICATIONS FOR 5 YR EXCLUSIVITY:	
Approved for NCE, no salt or ester of which previously approved	____

QUALIFICATIONS FOR 3 YR EXCLUSIVITY:			
Approval based on clinical study (other than BIO)?	Y X	N ___	
New Studies:			
Previously relied on by Agency for efficacy?	Y ___	N X	
Essential for Approval:			
Approval could have been based on literature?	Y ___	N X	
Previously approved in another application?	Y ___	N X	
Studies conducted by or for applicant:			
IND sponsored by applicant? or Certification of principal support?	Y X / Y ___	N ___ / N ___	

NOTE: If any checks appear in shaded area, it is likely that exclusivity should not be granted. Any recommendation contrary should be explained below:

_____

_____.

EXCLUSIVITY RECOMMENDED: 5 YR ____ 3 YR X NONE ____

CONCUR _____
NON CONCUR _____)

SIGNED _____
DIRECTOR, OFFICE OF DRUG STANDARDS

EXCLUSIVITY SUMMARY FOR NDA # ANDA 74-374 SUPPL # S-001

Trade Name PRIMSOL SOLUTION Generic Name TRIMETHOPRIM HCl

Applicant Name AXENT PEDIATRICS, INC HFD # 610

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1 (new indication)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Revised 5-90

cc: Original NDA Division File HFD-84

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

Page 2
revised
August 1990
This is the revised

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# TRIMPEX Tabs 100+200 mg N17-952

NDA# SEPTRA Susp (Sulfamethoxazole 200mg + Trimethoprim 40mg/5ml) N17-598

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /X/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /X/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

T-OM-01 _____

T-OM-02 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /X/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____ 6-5-97

Signature
Title: PROJECT MANAGER
BRANCH III
Date

_____ June 11, 1997

Signature of
Division Director
Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074374 /S001, S002

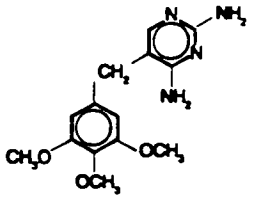
FINAL PRINTED LABELING

ASCENT®
PEDIATRICS, INC.

Primsol® Solution
(trimethoprim hydrochloride oral solution)
Dye-free, alcohol-free, flavored solution,
25 mg trimethoprim per 5 mL

DESCRIPTION

PRIMSOL (trimethoprim hydrochloride oral solution) is a solution of the synthetic antibacterial trimethoprim in water prepared with the aid of hydrochloric acid. Each 5 mL for oral administration contains trimethoprim hydrochloride equivalent to 25 mg trimethoprim and the inactive ingredients bubble gum flavor, methylparaben, propylparaben, propylene glycol, saccharin sodium, sucrose, water and hydrochloric acid to adjust pH to a range of 3.0 - 5.0. Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. Trimethoprim is a white to cream-colored, odorless, bitter compound with a molecular formula of $C_{14}H_{18}N_4O_3$ and a molecular weight of 290.32 and the following structural formula:



CLINICAL PHARMACOLOGY

Trimethoprim is rapidly absorbed following oral administration. It exists in the blood as unbound, protein-bound and metabolized forms. Ten to twenty percent of trimethoprim is metabolized, primarily in the liver; the remainder is excreted unchanged in the urine. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives. The free form is considered to be the therapeutically active form. Approximately 44% of trimethoprim is bound to plasma proteins.

Mean peak plasma concentrations of approximately 1 μg/mL occur 1 to 4 hours after oral administration of a single 100 mg dose. A single 200 mg dose will result in plasma concentrations approximately twice as high. The mean half-life of trimethoprim is approximately 9 hours. However, patients with severely impaired renal function exhibit an increase in the half-life of trimethoprim, which requires either dosage regimen adjustment or not using the drug in such patients (see DOSAGE AND ADMINISTRATION section). During a 13-week study of trimethoprim tablets administered at a dosage of 50 mg *q.i.d.*, the mean minimum steady-state concentration of the drug was 1.1 μg/mL. Steady-state concentrations were achieved within two to three days of chronic administration and were maintained throughout the experimental period.

Excretion of trimethoprim is primarily by the kidneys through glomerular filtration and tubular secretion. Urine concentrations of trimethoprim are considerably higher than are the concentrations in the blood. After a single oral dose of 100 mg, urine concentrations of trimethoprim ranged from 30 to 160 μg/mL during the 0- to 4-hour period and declined to approximately 18 to 91 μg/mL during the 8- to 24-hour period. A 200 mg single oral dose will result in trimethoprim urine concentrations approximately twice as high. After oral administration, 50% to 60% of trimethoprim is excreted in the urine within 24 hours, approximately 80% of this being unmetabolized trimethoprim.

Trimethoprim half-life, clearance, and volume of distribution vary with age. Excluding newborns, an apparent trend of increasing half-life, volume of distribution, and decreasing clearance is observed with increasing age until adulthood.

Since normal vaginal and fecal flora are the source of most pathogens causing urinary tract infections, it is relevant to consider the distribution of trimethoprim into these sites. Concentrations of trimethoprim in vaginal secretions are consistently greater than those found simultaneously in the serum, being typically 1.6 times the concentrations of simultaneously obtained serum samples. Sufficient trimethoprim is excreted in the feces to markedly reduce or eliminate trimethoprim-susceptible organisms from the fecal flora. The dominant non-*Enterobectenaceae* fecal organisms, *Bacteroides* spp. and *Lactobacillus* spp., are not susceptible to trimethoprim concentrations obtained with the recommended dosage.

Trimethoprim also concentrates into middle ear fluid (MEF) very efficiently. In a study in children aged 1 to 12 years, administration of a single 4 mg/kg dose resulted in a mean peak MEF concentration of 2.0 μg/mL.

Trimethoprim also passes the placental barrier and is excreted in breast milk.

Microbiology: Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. Thus, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

Trimethoprim has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic gram-positive microorganisms

Staphylococcus species	(coagulase-negative strains, including *S. saprophyticus*)
Streptococcus pneumoniae	(penicillin-susceptible strains)

Aerobic gram-negative microorganisms

Enterobacter species	
Escherichia coli	
Haemophilus influenzae	(excluding beta-lactamase negative, ampicillin resistant strains)
Klebsiella pneumoniae	
Proteus mirabilis	

NOTE: Moraxella catarrhalis isolates were found consistently resistant to trimethoprim.

Susceptibility Testing

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trimethoprim powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms isolated from urinary tract infections:

MIC (μg/mL)	Interpretation
≤ 8	Susceptible (S)
≥ 16	Resistant (R)

When testing *Haemophilus influenzae*[a]

MIC (μg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1 - 2	Intermediate (I)
≥ 4	Resistant (R)

When testing *Streptococcus pneumoniae*[b]

MIC (μg/mL)	Interpretation
≤ 2	Susceptible (S)
≥ 4	Resistant (R)

[a] Interpretive criteria applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1]

[b] Interpretive criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible

clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trimethoprim[a] powder should provide the following MIC values:

Microorganism		MIC (μg/mL)
Escherichia coli	ATCC 25922	0.5 - 2
Haemophilus influenzae[b]	ATCC 49247	0.06 - 0.5
Staphylococcus aureus	ATCC 29213	1 - 4
Streptococcus pneumoniae[c]	ATCC 49619	1 - 4

[a] Trimethoprim very medium-dependent.

[b] Range applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1]

[c] Range applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimatesof the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 μg trimethoprim to test the susceptibility of microorganisms to trimethoprim.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 μg trimethoprim[a] disk should be interpreted according to the following criteria for the indicated aerobic microorganism:

For testing aerobic microorganisms isolated from urinary tract infections:

Zone diameter (mm)	Interpretation
≥ 16	Susceptible (S)
11 - 15	Intermediate (I)
≤ 10	Resistant (R)

For testing *Haemophilus influenzae*[b]:

Zone diameter (mm)	Interpretation
≥ 16	Susceptible (S)
11 - 15	Intermediate (I)
≤ 10	Resistant (R)

[a] Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥ 20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

[b] Interpretative criteria applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[2]

Note:

Diffusion techniques are not recommended for determining susceptibility of *Streptococcus pneumoniae* to trimethoprim.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trimethoprim.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 μg trimethoprim[a] disk should provide the following zone diameters in this laboratory test quality control strain:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	21 - 28
Haemophilus influenzae[b]	ATCC 49247	27 - 33
Staphylococcus aureus	ATCC 25923	19 - 26

[a] Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥ 20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

[b] Range applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[2]

Note:

Diffusion techniques are not recommended for determining susceptibility of *Streptococcus pneumoniae* to trimethoprim.

INDICATIONS AND USAGE

PRIMSOL Solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Pediatric Patients:

Acute Otitis Media: For the treatment of acute otitis media due to susceptible strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*.
NOTE: *Moraxella catarrhalis* isolates were found consistently resistant to trimethoprim *in vitro*. Therefore, when infection with *Moraxella catarrhalis* is suspected, the use of alternative antimicrobial agents should be considered.
PRIMSOL is not indicated for prophylactic or prolonged administration in otitis media at any age.

Adults:

Urinary Tract Infections: For the treatment of initial episodes of uncomplicated urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter* species and coagulase-negative *Staphylococcus* species, including *S. saprophyticus*.

Cultures and susceptibility tests should be performed to determine the susceptibility of the bacteria to trimethoprim. Therapy may be initiated prior to obtaining the results of these tests.

CLINICAL STUDIES

The results of one multicenter, 30-day, comparative, randomized clinical trial without tympanocentesis in 262 pediatric patients with acute otitis media (AOM) are shown below. In this clinical trial, strict evaluability criteria were used to determine clinical response.

	PRIMSOL	SMX + TMP*
Enrolled	133	129
Evaluable	130	129
Clinical Cure	64/130 (49%)	63/129 (49%)
Clinical Improvement	30/130 (23%)	31/129 (24%)
Relapse/Recurrence	19/130 (15%)	18/129 (14%)
Outcome (based on 95% confidence interval)	[redacted]	PRIMSOL equivalent to TMP + SMX

*sulfamethoxazole + trimethoprim oral suspension

The results of an uncontrolled 30-day trial with tympanocentesis in 120 pediatric patients with AOM are shown below:

	Number of patients	
Enrolled	120	
Clinically Evaluable	102	
Microbiologically Evaluable	58	
Clinical Cure	50/102 (49%)	
Clinical Improvement	22/102 (22%)	
Clinical Relapse/Recurrence	20/102 (20%)	
Microbiologic Eradication Rates n= 58	Day 5 post- therapy	Day 20 post-therapy
Streptococcus pneumoniae	16/20 (80%)	14/20 (70%)
Haemophilus influenzae	14/17 (82%)	13/17 (77%)

Moraxella catarrhalis, isolated from five patients, were found consistently resistant to trimethoprim *in vitro*.

CONTRAINDICATIONS
PRIMSOL is contraindicated in individuals hypersensitive to trimethoprim and in those with documented megaloblastic anemia due to folate deficiency.

WARNINGS
Experience with trimethoprim alone is limited, but it has been reported rarely to interfere with hematopoiesis, especially when administered in large doses and/or for prolonged periods.

The presence of clinical signs such as sore throat, fever, pallor or purpura may be early indications of serious blood disorders.

PRECAUTIONS
General: Trimethoprim should be given with caution to patients with possible folate deficiency. Folates may be administered concomitantly without interfering with the antibacterial action of trimethoprim. Trimethoprim should also be given with caution to patients with impaired renal or hepatic function. If any clinical signs of a blood disorder are noted in a patient receiving trimethoprim, a complete blood count should be obtained and the drug discontinued if a significant reduction in the count of any formed blood element is found.

Drug Interactions: PRIMSOL may inhibit the hepatic metabolism of phenytoin. Trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 51% and decreased the phenytoin metabolic clearance rate by 30%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Drug/Laboratory Test Interactions: Trimethoprim can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of trimethoprim may also interfere with the Jaffé alkaline picrate reaction assay for creatinine resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with trimethoprim. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. No chromosomal damage was observed in human leukocytes cultured *in vitro* with trimethoprim; the concentration used exceeded blood levels following therapy with PRIMSOL. No adverse effects on fertility or general reproductive performance were observed in rats given trimethoprim in oral dosages as high as 70 mg/kg/day for males and 14 mg/kg/day for females.

Pregnancy:
Teratogenic Effects: Pregnancy Category C. Trimethoprim has been shown to be teratogenic in the rat when given in doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses 6 times the human therapeutic dose.

While there are no large well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and Pursell,[3] in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim plus sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received trimethoprim plus sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim may interfere with folic acid metabolism, PRIMSOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: The oral administration of trimethoprim to rats at a dose of 70 mg/kg/day commencing with the last third of gestation and continuing through parturition and lactation caused no deleterious effects on gestation or pup growth and survival.

Nursing Mothers: Trimethoprim is excreted in human milk. Because trimethoprim may interfere with folic acid metabolism, caution should be exercised when PRIMSOL is administered to a nursing woman.

Pediatric Use: The safety of trimethoprim has not been established in pediatric patients below the age of 2 months. The effectiveness of trimethoprim in the treatment of acute otitis media has not been established in patients below the age of 6 months.

ADVERSE REACTIONS
Adverse Events Reported During Pediatric Clinical Trials With PRIMSOL:
The following table lists those drug-related adverse events reported most frequently during the clinical trials in pediatric patients aged 6 months to 12 years. Most of these events were determined to be mild. The incidence of drug-related adverse events was significantly lower for PRIMSOL, which was most apparent for those events related to skin/appendages as a body system.

Drug-related Adverse Event	Percent of Pediatric Patients	
	PRIMSOL (N=310)	SMX+TMP* (N=197)
Body as a whole		
abdominal pain	<1	2.5
Digestive system		
diarrhea	4.2	4.6
vomiting	1.6	1.5
Skin/Appendages		
rash	1.3	6.1

*sulfamethoxazole + trimethoprim oral suspension

An increase in lymphocytes and eosinophils was noted in some pediatric patients following treatment with PRIMSOL or sulfamethoxazole + trimethoprim oral suspension.

Adverse Reactions Reported For Trimethoprim:
In addition to the adverse events listed above which have been observed in pediatric patients receiving PRIMSOL, the following adverse reactions and altered laboratory tests have been previously reported for trimethoprim and therefore, may occur with PRIMSOL therapy:
Dermatologic reactions: pruritus and exfoliative dermatitis. At the recommended adult dosage regimens of 100 mg *b.i.d.*, or 200 mg *q.d.*, each for 10 days, the incidence of rash is 2.9% to 6.7%. In clinical studies which employed high doses of trimethoprim in adults, an elevated incidence of rash was noted. These rashes were maculopapular, morbilliform, pruritic and generally mild to moderate, appearing 7 to 14 days after the initiation of therapy.
Gastrointestinal reactions: Epigastric distress, nausea, and glossitis.
Hematologic reactions: Thrombocytopenia, leukopenia, neutropenia, megaloblastic anemia and methemoglobinemia.
Metabolic reactions: Hyperkalemia, hyponatremia.
Miscellaneous reactions: Fever, elevation of serum transaminase and bilirubin, and increases in BUN and serum creatinine levels.

OVERDOSAGE
Acute: Signs of acute overdosage with trimethoprim may appear following ingestion of 1 gram or more of the drug and include nausea, vomiting, dizziness, headaches, mental depression, confusion and bone marrow depression (see CHRONIC OVERDOSAGE).

Treatment consists of gastric lavage and general supportive measures. Acidification of the urine will increase renal elimination of trimethoprim. Peritoneal dialysis is not effective and hemodialysis only moderately effective in eliminating the drug.

Chronic: Use of trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, trimethoprim should be discontinued and the patient should be given leucovorin, 3 to 6 mg intramuscularly daily for three days, or as required to restore normal hematopoiesis.

DOSAGE AND ADMINISTRATION

Acute Otitis Media in Pediatric Patients: The recommended dose for pediatric patients with acute otitis media is 10 mg/kg trimethoprim per 24 hours, given in divided doses every 12 hours for 10 days. The following table is a guideline for the attainment of this dosage:

Pediatric patients 6 months of age or older:

Weight		Dose (every 12 hours)	
lb	kg	tsp	mL
11	5	1	5
22	10	2	10
33	15	3	15
44	20	4	20
55	25	5	25
66	30	6	30
77	35	7	35
≥88	≥40	8	40

Uncomplicated Urinary Tract Infections: The usual oral adult dosage is 100 mg (20 mL) every 12 hours or 200 mg (40 mL) every 24 hours, each for 10 days.

Patients with Impaired Renal Function: The use of trimethoprim in patients with a creatinine clearance of less than 15 mL/min is not recommended. Patients with a creatinine clearance of 15 to 30 mL/min should receive half the dose recommended for patients of the same age with normal renal function.

HOW SUPPLIED

PRIMSOL (trimethoprim hydrochloride oral solution), dye-free, alcohol-free, bubble gum flavored, containing trimethoprim hydrochloride equivalent to 25 mg of trimethoprim in each 5 mL: bottle of 400 mL (13.5 fl oz). NDC 59439-477-02. Store between 15°-25°C (59°-77°F). Dispense in tight, light-resistant glass or PET plastic containers as defined in USP. Dispense with enclosed dose cup. Do not dispense if tamper-evident neck seal is broken prior to initial use.

Caution - Federal law prohibits dispensing without prescription.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
3. Brumfitt W, Pursell R. Trimethoprim/Sulfamethoxazole in the Treatment of Bacteriuria in Women, *J Infect Dis* 128 (suppl): S657-S663, 1973.

Revised April 2, 1997.

Manufactured for Ascent Pediatrics, Inc., Wilmington, MA 01887 by Lyne Laboratories, Inc., Brockton, MA 02401

U. S. Patent pending, serial number 07/772,926

NDC 59439-477-02

Primsol®
Solution

(trimethoprim hydrochloride oral solution)

trimethoprim, 25 mg/5 mL

For important prescribing information, read accompanying package insert.

CAUTION: Federal law prohibits dispensing without prescription

Store between 15° - 25°C (59° - 77°F)

400 mL (13.5 fl oz)

ASCENT PEDIATRICS, INC.

Pharmacist: Dispense in tight, light-resistant glass or PET plastic containers as defined in USP.

Dispense with enclosed dose cup.

Do not dispense if tamper-evident neck seal is broken prior to first use.

APPROVED JUN 17 1997

Manufactured for
Ascent Pediatrics, Inc.
Wilmington, MA 01887
by
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L1A0397

Primsol® Solution
(trimethoprim hydrochloride oral solution)
trimethoprim, 25 mg/5 mL

NDC 59439-477-02

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JUL 17 1997

C1A0397

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074374 /S001, S002

MICROBIOLOGY REVIEW

Consultative Review for HFD-650
(Division of Bioequivalence)
Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiological Review #1

Requestor: Larry Galvin, OGD/HFD-650

Reason for Request: Microbiological review of the antimicrobial activity of the drug product.

NDA #74-374 **DATE COMPLETED: 12/24/96**

APPLICANT:
Ascent Pharmaceuticals, Inc.
9 Linnell Circle
Billerica, Massachusetts 01821

2 0 1997

CONTACT PERSONS:
Robert W. Mendes, Ph.D.,
Vice President, Regulatory Affairs
Director, New Technology
Tel: (508)--667-6300

SUBMISSION REVIEWED:
PROVIDING FOR:
In the treatment of the indications of Acute Otitis Media (under the age 12)

PRODUCT NAMES(S):

Proprietary:	PRIMSOL® Solution
Non-Proprietary/USAN:	Trimethoprim Hydrochloride Oral Solution
CAS No.:	*CAS-2738-70-5*

CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA, MOL. WT.:
Trimethoprim:

Chemical Name	=	See 1996 USAN (Page 725)
Molecular Formula	=	$C_{14}H_{18}N_4O_3$
Molecular Weight	=	290.32

DOSAGE FORM: Solution

ROUTE OF ADMINISTRATION: Oral

STRENGTH: 5 mg trimethoprim/mL;
(= 25 mg trimethoprim/5 mL)

PHARMACOLOGICAL CATEGORY: 3S
Antibacterial agent (dihydrofolate reductase inhibitor agent)

DISPENSED: ___x___ **Rx** _____ **OTC**

INITIAL SUBMISSION: 12/29/95
Received by OGD: 1/03/96
Letter Date: 12/29/95
Received by CDER: 2/27/96

AMENDMENT(S) and Other Documents: Ascent FAX on labeling, dated 3/14/97.

PATENT:
Ascent believes, after approval of the application, will entitle the applicant to be granted a 3-year marketing exclusivity under the provisions of 21 CFR §314.50(j) and 21 CFR §314.108(b)(4), respectively.

RELATED DOCUMENTS:
Trimethoprim hydrochloride, approved on 6/23/95.

COMMENTS:
NDA 70-495, Trimethoprim Tablets, Oral, 200 mg, approved on 9/24/86.

This drug is the subject of the compendial monograph, 23 USP (Trimethoprim) on page 1602. [Note: 23 USP (Sulfamethoxazole) on page 1461, and 23 USP (Sulfamethoxazole and Trimethoprim Oral Suspension) on pages 1463 and 1464, respectively.

CONCLUSIONS:

From the clinical microbiology perspective, Ascent Pharmaceuticals, Inc, should be notified that NDA 74-374 is "approvable" for acute otitis media. [See **PACKAGE INSERT** and the corresponding subsections, on pages 42 to 48.]

TABLE OF CONTENTS

INTRODUCTION

Trimethoprim (TMP) has a highly selective inhibitory activity against dihydrofolate reductase. Dihydrofolate reductase is essential for DNA synthesis in many pathogens, especially those responsible for urinary and respiratory tract infections in man.

TMP, itself, has been considered for the treatment of urinary and respiratory tract infections.

Previously, TMP has been used a potentiator of sulfonamide activity.

Brumfitt and Hamilton-Miller (1) determined that TMP is ~ 20-fold more active than SMX *in vitro*. TMP penetrates human tissues much more efficiently than SMX. The TMP concentration is generally higher in the tissues than the corresponding concentration in plasma.

TMP has been approved in the USA for treating uncomplicated urinary tract infection for patients 12 years of age and older. The applicant is conducting clinical trials for acute otitis media in children 6 to 12 years of age.

PRECLINICAL EFFICACY (*in vitro*)

In general, when given orally, trimethoprim (TMP) is well absorbed from the gut and is distributed in tissues and body fluids (including the middle ear fluid). Approximately, 65 to 70% TMP is protein bound. Approximately 50 to 60% TMP (or metabolites) is excreted in the urine within 24-hours.

MECHANISM OF ACTION

The antibacterial activity of TMP is essentially due to its inhibition of the bacterial enzyme "dihydrofolate reductase" (DHFR). The conversion of dihydrofolate to tetrahydrofolate (precursor of folic acid) is interfered by TMP. The biosynthesis of purine and DNA in the bacterium are both affected. If the DHFR is completely inhibited, thymine starvation ensues resulting in bacterial death. As compared in activity against the human enzyme, TMP is ~ 10,000 times more active against the bacterial DHFR. Humans require folic acid in their diet, however they do not synthesize it. Brumfitt and Hamilton-Miller determined that purine synthesis is not affected significantly by the enzyme inhibition by TMP. This is especially true when using adult doses ≤ 400 mg in daily used therapeutically in susceptible bacterial infections.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

It has been demonstrated in *in vitro* studies that trimethoprim (TMP) is highly active against a wide range of pathogenic bacteria, for example, those that cause infections of the urinary and respiratory tracts. Combination therapy, TMP and sulfamethoxazole (SMX) was introduced into the USA in the 1970's. Some believed that the aforementioned combination therapy was superior than the individual therapies in treating UTI and respiratory infections. Other investigators, Brumfitt and Hamilton-Miller (1) have published literature questioning the aforementioned premise.

There is some evidence of *in vitro* synergism between TMP and SMX for antibacterial activity. However, in patients, the synergism has not been shown. In *in vitro* studies, Brumfitt and Hamilton-Miller (1) determined that TMP is ~ 20 times more active than SMX against UTI pathogens. Brumfitt and Hamilton-Miller also determined that TMP penetrates human tissues much more efficiently than SMX. The TMP concentration is greater in tissue than in the corresponding plasma. The investigators, Koch et al. (2), Kasanen et al. (3), and the Trimethoprim Study Group (4) investigated and determined that TMP alone is as effective as TMP+SMX for the treatment of uncomplicated UTI and for recurrent and complicated infections.

Lewis, Anderson, and Lacey (5) observed that in *in vitro* antibacterial activity in the urine could be accounted for by the TMP content following TMP+SMX dosing. It was believed that the clinical effectiveness was largely due to the TMP component (and not the TMP+SMX combination).

TABLE 1*

TMP *in vitro* Activity Against Otitis Media Pathogens

Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes and *Staphylococcus aureus* are the most common microorganisms associated with acute otitis media in children.

The drug therapy combination, TMP+SMX has been approved for the treatment of children with acute otitis media due to susceptible strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*, respectively (the two most common causative agents). In TABLE 2, the antibacterial activity of TMP and SMX for the aforementioned pathogens and others involved in otitis media is provided.

TABLE 2*

In Vitro Activity Reported for Trimethoprim (TMP) and Sulfamethoxazole (SMX) Against pathogens Associated with Otitis Media

	Minimum Inhibitory Concentration (mcg/mL)				
Reference	*S. pneumoniae*	*H. influenzae*	*M. catarrhalis*	*S. pyogenes*	*S. aureus*
1. PDR					
TMP	0.15-1.5	0.15-1.5	----	----	----
SMX	7.35-24.5	2.85-95.0	----	----	----
2. Le,CT					
TMP	0.1-0.3	0.125	0.25-2.5	----	----
3. Braude, AI					
TMP	2.0	1.0	----	1.0	1.0
SMX	30.0	10.0	----	100.0	3.0
4. Zinner & Mazer					
TMP	0.004-5.0	0.1-12.5	----	0.02-1.0	0.15-2.0
5. Bushy, SRM					
TMP	1.0	0.12	----	0.4	0.2
SMX	32.0 (±16)	>50.0	----	100.0 (±25)	4.0

1. PDR. 1993:833-834,1973-1974.
2. *Contemp. Pediat.* 1991: **8**:11-30.
3. Infectious Diseases and Medical Microbiology. 1986; 2nd Ed., Saunders:175-197.
4. *Anti-Infective Therapy.* 1986; John Wiley:235-254.
5. *Postgrad Med J.* 1969:**45**:(Suppl.)10-18.

* Quantitative MIC values were not provided in the cited reports. Adapted from NDA 74-374, Vol. 2, Table 2, on Page 02-021.

TABLE 3 shows the MIC results (7) for various isolates from the Boston City Hospital for TMP and SMX.

TABLE 3*

Susceptibility of Various Strains of Bacteria to TMP and SMX

Microorganism	No. Strains	TMP MIC (mcg/mL) Range	TMP MIC (mcg/mL) Median	SMX MIC (mcg/mL) Range	SMX MIC (mcg/mL) Median
S. pneumoniae	33	0.04-0.8	0.4	6.3->1000	50
H. influenzae	35	0.1-12.5	0.8	25->1000	1000
S. pyogenes	35	0.02-0.8	0.1	3.1-1000	12.5
S. aureus	36	0.4-1.6	0.8	25->100	50
S. epidermidis	35	0.2-6.3	0.4	12.5->1000	100

* Adapted from NDA 74-374, Vol. 2, Table 3, on Page 02-022.

In the aforementioned TABLE 3, TMP alone was found to be active in clinically useful concentrations against most of the important pathogens in otitis media.

RESISTANCE TO TRIMETHOPRIM (TMP)

A number of mechanisms of resistance for trimethoprim (TMP) have been identified. The various mechanisms of resistance include the following: 1) Bacterial membrane impermeability, 2) hyperproduction of the dihydrofolate reductase (DHFR) by resistant bacteria, and 3) production of R-plasmid encoded DHFR insensitive to TMP inhibition. [Brumfitt and Hamilton-Miller (1) and Grey, Hamilton-Miller, and Brumfitt (8)]

The most studied mechanism (and maybe the most common) of resistance for trimethoprim is the R-factor mediated resistance. The plasmid encoded synthetases in resistant bacteria generally have elevated K_i for TMP. The bypass system allows the microorganism to survive in the presence of high concentrations of TMP.

Several different TMP-resistant DHFR isozymes have been isolated, and like many drug resistant determinants, Brumfitt and Hamilton--Miller (1) found out that these characters may be encoded by transposons.

It is not uncommon for simultaneous resistance to both trimethoprim and sulfonamides. This may indicate that two R-mediated bypass enzymes can exist in the same bacterium. Huovinen et al. (9) studied the mechanism of TMP and determined that the common occurrence of sulfonamide resistance genes in genetic linkage with TMP resistance genes largely invalidates the argument for using the combination of the 2-drugs to prevent development of resistance.

In another study, Sundstrom et al. (10) reported a new plasmid borne gene, dhfrVIII, encoding high-level TMP resistance (Tp^R) in an intestinal *Escherichia coli*. The new gene is a widely occurring mediator of TpR. Among 973 examined Tp^R *Escherichia coli*, the new resistance gene (dhfrVIII) was found in 13 (1.3%) isolates from Sweden, Finland, and Nigeria. The new gene was sequenced and found to code for a DHFR of 169 amino acids. Davies (11) studied also the mechanism of antimicrobial resistance and found that some bacterial species may become resistant to TMP and sulfamethoxazole by undergoing mutations in The C1 metabolism pathway (thereby eliminating their dependence on thymine as an exogenous source).

To collect more information on the extent of bacterial resistance to TMP several surveys were performed. Grey, Hamilton-Miller, and Brumfitt (8) investigated and found that even though the overall incidence of bacterial resistance to TMP was 3.2% in > 4000 bacterial strains isolated from urine samples, only 1.4% of *Escherichia coli* were resistant to TMP between 1972 and 1975. In another study (1979), Hamilton-Miller, Gooding, and Brumfitt (12) showed that the overall incidence of resistance rose to 11.5% (and for *E. coli* resistance rose to 7.1%). In addition, specific R-factor mediated resistance among resistant bacteria had risen from 10% (1975) to 60% (1979). Later, in another survey (1981), Brumfitt, Hamilton-Miller, and Wood (13) found the incidence at 12.2% had not significantly changed, and virtually all the resistance observed was found due to R-factors. The aforementioned investigators and Amyes, Emmerson, and Smith (14)] reported that there was no evidence that the increased incidence of resistance to TMP was connected with the introduction of TMP alone for clinical use.

In addition, the aforementioned, investigators performed surveys in 1985 and 1991 and calculated that *Staphylococcus saprophyticus* was resistant to TMP ~ 17 of 186 isolates (= 9%) and 2 of 96 isolates (= 2%) in those years, respectively.

Studies from all over the world have reported resistance of *Streptococcus pneumoniae* to penicillin. It is believed that some highly resistant *S. pneumoniae* are also resistant to cephalosporins, non-beta-lactam antibiotics (erythromycin, tetracycline, chloramphenicol, trimethoprim, and sulfamethoxazole). The applicant references the following, as support: Friedland and McCracken (15), Klien (16), Doern (17), McCracken (18), Kaplan and Mason (19), and Pikis et al. (20), respectively.

PRECLINICAL EFFICACY (*in vivo*)

PHARMACOKINETICS/BIOAVAILABILITY

Middle Ear Fluid (MEF) Penetration

Kasanen et al. (3) found that trimethoprim (TMP) concentrates in tissues, including the middle ear fluid (MEF) very efficiently. Krause et al. (21) studied the penetration of 4-antibiotics in MEF by the administration of a single oral dose to children, ages 1 to 12 years, with chronic serous otitis media. Twenty-three children received TMP+SMX combination (TMP = 4 mg/kg and SMX = 20 mg/kg), 19 received amoxicillin, 26 received cefaclor, and 15 received an erythromycin (ER) - sulfisoxazole combination therapy. In TABLE 4, the mean peak concentrations of the aforementioned antibiotics in MEF and the values obtained as percentages of peak serum concentrations are shown.

TABLE 4*

Concentration of Antibiotics in Middle Ear Fluid (MEF)

Antibiotic	Mean Peak Conc. in MEF (mcg/mL)	Percentage (%) of Peak Serum Conc.
TMP+SMX		
TMP	2.0	65
SMX	18.7	27
Amoxicillin	5.6	41
Cefaclor	3.8	23
ER+SSX		
ER	None Detected	--
SSX	20.9	20

* Adapted from NDA 74-374, Vol. 2, Table 4, on Page 02-022.

It can seen that trimethoprim (TMP) from the aforementioned TABLE 4 had only a mean peak concentration (= 2.0 mcg/mL) in the middle ear fluid, however had the highest percentage of peak serum concentration (= 65%) compared to all the other antibiotics [even sulfamethoxazole (SMX) = 27%].

Krause et al. (21) also calculated the ratios of MEF concentrations to the MIC values for 3-microorganisms (*Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes*). It was seen that the higher the MEF:MIC ratio, the greater the effective therapeutic concentration in the middle ear. The MEF:MIC calculated ratio results are shown in TABLE 5.

TABLE 5*

Ratios of Antibiotic Concentrations in MEF to MIC

	MEF:MIC Ratio			
		H. Influenzae		
Antibiotic	***S. pneumoniae***	**AM-Sus.**	**AM-Res.**	***S. pyogenes***
Amoxicillin	112	28	--	224
Cefaclor	15	0.6	0.5	29
TM+SMX				
TM	20	67	33	40
SMX	9	32	16	19

AM Sus. = Ampicillin Susceptible
AM Res. = Ampicillin Resistant

* Adapted from NDA 74-374, Vol 2, Table 5, on Page 02-023.

It can be seen from TABLE 5 that amoxicillin had the highest MEF:MIC ratios for *S. pneumoniae* and *S. pyogenes*. However, trimethoprim (TMP) was superior to amoxicillin in MEF:MIC ratio for *H. influenzae* and was second only to amoxicillin in MEF:MIC ratio for *S. pneumoniae* and *S. pyogenes*, respectively.

In another study, from 23 patients with chronic secretory otitis media, investigators Kohonen, Palmgren, and Renkonen (22), obtained 39 middle ear fluid samples. This was after the patients were administered 3-doses of TMP (= 3 mg/kg) and sulfadiazine (= 5 mg/kg). The middle ear fluid samples were obtained 80 to 270 minutes (mean = 142 minutes) after the last dose. The mean concentrations of the 2-drugs (TMP and sulfadiazine) are shown in the following TABLE 6.

TABLE 6*

Concentrations in Middle Ear Fluid (mcg/mL)

	TMP	Sulfadiazine
Mean	1.62	10.54
Range	0.8-3.5	0-25.0

* Adapted from NDA 74-374, Vol. 2, table 6, on Page 02-023.

The investigators observed that the MEF levels (TABLE 6) exceeded the usual MIC values for *S. pneumoniae* and *H. influenzae*.

Nelson et al. (23), in another study,, randomized 37 children undergoing tympanotomy to receive a single dose of the following antibacterial drugs: penicillin V, amoxicillin, erythromycin estolate, erythromycin ethylsuccinate, cefaclor or TMP+SMX. The investigators reported that the mean concentrations of all the drugs in MEF were several-fold greater than the usual MICs for *Streptococcus pneumoniae*. Trimethoprim and cefaclor were the only 2-antibacterial drugs' concentrations in the MEF greater than the known MICs for *Haemophilus influenzae*.

CLINICAL EFFICACY (Clinical Microbiology)

ISOLATES/RELEVANCE TO APPROVED INDICATIONS

Ascent contracted of the located in to conduct 2-*in vitro* microbiology studies using trimethoprim (TMP) and the combination trimethoprim/sulfamethoxazole (T/S) against *Haemophilus influenzae* and *Streptococcus pneumoniae*.

The purpose of the 2 studies were to:

1. Assess the *in vitro* effectiveness of TMP against *H. influenzae* and *S. pneumoniae*,

2. Develop *in vitro* interpretive criteria for testing susceptibility of the 2 aforementioned microorganisms to TMP,

3. Define quality control parameters for susceptibility testing of *H. influenzae* and *S. pneumoniae* to TMP; and

4. Correlate the *in vitro* susceptibility data with the *in vivo* clinical response data from the otitis media trial in children.

MIC BROTH/AGAR DILUTION COMPARISONS, MIC/DISK DIFFUSION CORRELATION STUDIES, AND QUALITY CONTROL STUDIES (MIC AND DISK DIFFUSION)

In the first study, "Quality Control Parameters for Susceptibility Testing of *Haemophilus influenzae* and *Streptococcus pneumoniae* to Trimethoprim by Broth Microdilution and Disk Diffusion Methods", the clinical investigators, investigated quality control parameters for trimethoprim. The investigators used the quality microorganisms *Haemophilus influenzae* ATCC 49247 and *Streptococcus pneumoniae* ATCC 49619 when testing by the broth microdilution and disk diffusion methods, respectively.

The broth microdilution susceptibility method was performed according to NCCLS (M7-A3). The applicant provided the test agent, trimethoprim (TMP), and the control agent, trimethoprim/sulfamethoxazole (T/S), respectively. *Haemophilus* Test Medium (HTM) supplemented with 0.2 U/mL thymidine phosphorylase was used for testing *H. influenzae*. Mueller-Hinton broth with 2-3% lysed horse blood was used for testing *S. pneumoniae*. For testing the trimethoprim, concentrations of trimethoprim tested were 2-fold dilutions ranging from 4.0 to 0.016 μg/mL. For testing the T/S, a 1/19 ratio of the 2-components (T/S) was used, with the TMP concentration matching those of TMP alone.

The disk diffusion method was performed according to NCCLS (M2-A5). The applicant provided commercial 5 μg trimethoprim (TMP) test disks and 1.25/23.75 μg trimethoprim/sulfamethoxazole (T/S) control disks. Commercial 5 μg trimethoprim test disks and 1.25/23.75 μg T/S control disks were used. HTM agar was used for testing *H. influenzae* and Mueller-Hinton blood agar was used for testing *S. pneumoniae*, respectively.

Ten laboratories (Vol. 2, Table 1, "List of Participants and Affiliations", on page 02-238) participated in the study. The "Study Design and Procedure" is fully described in NDA 74-374, Vol. 2, on pages 02-232 & 02-233. Each laboratory received broth microdilution panels containing dilutions of either TMP or T/S in HTM broth; broth microdilution panels containing dilutions of either TMP or T/S in Mueller-Hinton broth with lysed horse blood; HTM agar plates; Mueller-Hinton blood agar plates; 5 μg trimethoprim disk cartridges; and 1.25/23.75 μg T/S disks.

The procedure by each of the 10 laboratories was performed on 15 separate days. The results generated the following: 600 TMP MIC determinations for *H. influenzae*, 600 MICs for *S. pneumoniae*, 150 T/S MICs for each microorganism, and 600 zone diameter results for both TMP and T/S against *H. influenzae*, and 900 for each against *S. pneumoniae*, respectively. The results were analyzed by the method of Barry (1989) for MIC parameters, and Gavan et al.(24) for zone diameter parameters.

Investigators' Comments and Recommendations:

1. *Haemophilus influenzae* ATCC 49247

a. Broth Dilution Susceptibility Results:

The investigators indicated that all the 150 T/S MIC susceptibility results on *H. influenzae* ATCC 49247 fell within the acceptable NCCLS published range: M100-S5 (M7-A3, Vol. 14, No. 16, 1994) = 0.03/0.57 to 0.25/4.75 μg/mL. [Note: M100-S7 (M7-A4, Vol. 17, No. 2, 1997) = 0.03/0.59 to 0.25/4.75 μg/mL.] That the 600 trimethoprim MIC determinations on *H. influenzae* ATCC 49247 fell within a 4-dilution range of 0.06 to 0.5 μg/mL. As seen in Vol. 2, Figure 1, on page 02-239, the pattern was bimodal. Media lot to lot variations and disk lot variations were not observed. Data are provided in Vol. 2, Appendix A (Microdilution Tests), on pages 02-254 to 02-277.

b. Disk Diffusion Susceptibility Results:

582 out of 600 (= 98.7%) T/S disk zone diameter measurements were within the NCCLS acceptable quality control range: M100-S5 (M2-A5, Vol. 14, No. 16, 1994) = Disk Content = 1.25/23.75 μg; Zone Diameter = 24 to 32 mm). [Note: M100-S7 (M2-A6, Vol. 17, No. 1, 1997) = Disk Content = 1.25/23.75 μg; Zone Diameter = 24 to 32 mm]. As seen in Vol. 2, Figure 2, on page 02-240, the 600 TMP zone diameters had an almost bell-shaped distribution with a modal value = 30 mm. 98.7% of all results fell within a 7 mm range of 27 to 33 mm. Because of the higher content (and consequently greater activity) of TMP in the commercial TMP disk (= 5 μg) as compared to the commercial T/S disk (= 1.25 μg), the aforementioned TMP range extends 2 mm larger than that approved for T/S. Again, media lot to lot variations were not observed. Data are provided in Vol. 2, Appendix A (Zone Diameters), on pages 02-278 to 02-289.

2. *Streptococcus pneumoniae* ATCC 49619

a. Broth Dilution Susceptibility Results:

The investigators indicated that all the 150 T/S MIC susceptibility results on *S. pneumoniae* ATCC 49619 also fell within the acceptable NCCLS published range: M100-S5 (M7-A3, Vol. 14, No.16, 1994) = 0.12/2.3 to 1/19 μg/mL. [Note: M100-S7 (M7-A4, Vol. 17, No. 2, 1997) = 0.12/2.4 to 1/19 μg/mL.] 555 out of the 600 (= 99.2%) trimethoprim MIC determinations on *S. pneumoniae* ATCC 49619 fell within a 3-dilution range of 1.0 to 4.0 μg/mL. and the modal TMP MIC was 2.0 μg/mL (See Vol. 2, Figure 3, on page 02-241.) Again, media lot to lot significant variations were not observed. Data are provided in Vol. 2, Appendix C (Microdilution Tests), on pages 02-290 to 02-301.

b. Disk Diffusion Susceptibility Results:

The NCCLS acceptable quality control range: M100-S5 (M2-A5, Vol. 14, No. 16, 1994) = Disk Content = 1.25/23.75 μg; Zone Diameter = 22 to 27 mm). [Note: M100-S7 (M2-A6, Vol. 17, No. 1, 1997) = Disk Content = 1.25/23.75 μg; Zone Diameter = 22 to 27 mm].

There were problems with the disk diffusion results. The modal zone diameter was 30 mm (see NCCLS: "acceptable" range = 22 to 27 mm). As seen in Vol. 2, Figure 4, on page 02-242, the distribution of the results was much boarder and nearly bimodal, with only 359 (= 40%) results falling within the "acceptable" range. Media effect and poor definition of the zone margin were attributed for the board distribution range of results. The 10 different laboratories each had good intralaboratory reproducibility with each medium (ranges = 2 to 8 mm), However the interlaboratory reproducibility was very poor with modal values ranging from 27 to 35 mm. In Vol. 2, Figures 5 to 7, on pages 02-243 to 02-245, the 3-lots of media used, 2 had modal zone diameters of 30 mm (Figures 5 & 7) and one (Figure 6) was 24 mm. Data are provided in Vol. 2, Appendix D (Zone Diameters) Trimethoprim/Sulfamethoxazole), on pages 02-302 to 02-312.

In Vol. 2, Figure 8, on page 02-246, there is a clear bimodal (15 mm & 20 mm) distribution. There were significant differences between media: As seen in Vol 2: Figure 9 (mode = 20 mm), Figure 10 (mode = 14 mm), and Figure 11 (mode = 19 mm), on pages 02-247 to 02-249, respectively. There were no significant differences between the different lots of disks. However, there was considerable variation among the 10 laboratories' results. The individual laboratory range varied from 2 to 11 mm with individual lots. Data are provided in Vol. 2, Appendix E (Zone Diameters) Trimethoprim, on pages 02-313 to 02-323.

At this time, the investigators are reluctant to recommend quality control ranges for TMP against *S. pneumoniae*. They even question the current ranges for T/S. The investigators indicate that there are problems related to the medium and the endpoint interpretation. The 2-aforementioned problems need to be resolved before QC parameters can be recommended.

There are significant effects of media on T/S and trimethoprim disk tests. The investigators decided to test 31 *S. pneumoniae* isolates by agar dilution using 3-lots of Mueller-Hinton with 5% sheep blood. The results showed that the T/S MICs on lot #1 were nearly twice (1.61 times) those of lot #2. MICs of lot #3 were 2.13 times of lot #2 (Vol. 2, Table 2, "Agar vs Microbroth Dilution for *S. pneumoniae* vs SXT", on page 02-250). The TMP MICs were less pronounced: MICs on lot #1 were 1.55 times those on lot #2, and lot #3 MICs were 1.47 times those of lot #2 (Vol. 2, Table 3, "Agar vs Microbroth Dilution for *S. pneumoniae* vs TMP", on page 02-251).
The interpretation of the effect of the media was uncertain because of the smaller number (16) of *H. influenzae* tested and that several strains failed to grow on the agar dilution plates. As seen in Vol. 2, Table 4, "Agar vs Microbroth Dilution for *H. influenzae* vs SXT", and Table 5, "Agar vs Microbroth Dilution for *H. influenzae* vs TMP", on pages 02-252 & 02-253, the differences in agar dilution MICs between media was minimal for both drugs and the results were within 1-dilution of those by broth microdilution.

Investigators' Conclusions:

From the results of their study, the 2-investigators, recommended the following trimethoprim quality control ranges for *Haemophilus influenzae* ATCC 49247 and *Streptococcus pneumoniae* ATCC 49619, respectively:

1. *Haemophilus influenzae* ATCC 49247:

TMP MIC range	=	0.06 to 0.5 μg/mL
TMP zone diameter range	=	27 to 33 mm

2. *Streptococcus pneumoniae* ATCC 49619:

TMP MIC range	=	1.0 to 4.0 μg/mL
TMP zone diameter range	=	At this time, no recommendation.

Clinical Microbiology Reviewer's Conclusions:

This Clinical Microbiology Reviewer agrees with the recommended quality control ranges (MICs and Zone Diameter Sizes) for *Haemophilus influenzae* ATCC 49247 and *Streptococcus pneumoniae* ATCC 49619, respectively.

IN VITRO STUDIES CONDUCTED DURING THE CLINICAL TRIALS

Haemophilus influenzae and *Streptococcus pneumoniae* Studies

The applicant performed the following clinical trials to assess the safety and efficacy of the drug product in children:

Open Trial of PRIMSOL® Solution (Trimethoprim) Utilizing Tympanocentesis in Pediatric Patients with Acute Otitis Media (Study and Protocol No. T-OM-01):

Middle Ear Aspirate Cultures and Susceptibility Testing

At the time of the clinical trial studies, NCCLS had no zone diameter interpretive criteria[a] standard recommendations against the tested microorganisms: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The investigators used those NCCLS recommendations (TABLE 7) for the trimethoprim/sulfamethoxazole drug combination, as follows:

TABLE 7*

NCCLS Zone Diameter Interpretive Standards

Drug	Disk Content
Trimethoprim	5 μg
Trimethoprim/sulfamethoxazole	1.25/23.75 μg

	Zone Diameter (mm)		
Microorganism	Susceptible	Intermediate	Resistant
Streptococcus pneumoniae[a]	≤ 10	11-15	≥ 16
Haemophilus influenzae	≤ 10	11-15	≥ 16
Moraxella catarrhalis	≤ 10	11-15	≥ 16

* Adapted from NDA 74-374, Vol 2, Table 1, on Page 02-381.

a. Currently, diffusion techniques (zone diameters) are not recommended for the testing of *S. pneumoniae* by both NCCLS and the applicant's consultants (Fuchs and Barry).

Middle Ear Isolates (Primary Pathogens)-Informational Only*

Those patients (n=120) with signs and symptoms of acute otitis media underwent tympanocentesis. The procedure was to isolate the primary/causative pathogen from middle ear effusion. Sometimes the procedure was performed in both patient's ears. From 54 patients, at least one (1) primary pathogen was recovered. Sometimes other isolates than the 3-primary pathogens were recovered. Sixty-six (66) primary isolates were recovered from 54 patients. The clinical information and results (TABLE 8) are as follows:

TABLE 8**

Primary Pathogens from Middle Ear Effusions of Patients with Acute Otitis Media

No. patients undergoing tympanocentesis:	120
No. patients with at least one (1) primary pathogen:	54
No. patients with more than one (1) primary pathogen:	7

Primary Pathogens Susceptibility Testing for TMP
Zone Diameter (mm)

Pathogen	No. Isolates	Susceptible	Resistant	Not Done
S. pneumoniae	34	28	4	2
H. influenzae	27	20	7	0
M. catarrhalis	5	0	5	0
Total =	66	48	16	2

One (1) isolate *H. influenzae*, susceptible to TMP + SMX, not tested against TMP alone.

* NCCLS breakpoints on trimethoprim+/sulfamethoxazole were used. Currently, diffusion techniques (zone diameters) are not recommended for the testing of *S. pneumoniae* by both NCCLS and the applicant's consultants (Fuchs and Barry).

** Adapted from NDA 74-374, Vol 2, Table 2, on Page 02-382.

The clinical trial susceptibility results show that 28/34 (82%) *Streptococcus pneumoniae* isolates and 20/27 (74%) *Haemophilus influenzae* isolates were susceptible to TMP. However, all (5/5 = 100%) of the *Moraxella catarrhalis* isolates were resistant to TMP.

In Vitro Interpretive Criteria Studies

Background:

There has been an increase in the resistance of upper respiratory pathogens (*Haemophilus influenzae* and *Streptococcus pneumoniae*) to the β-lactam antibiotics. Currently, trimethoprim/sulfamethoxazole (T/S) has shown to be effective against the respiratory pathogens. However, there are incidences of allergy to the sulfamethoxazole drug component.

Therefore the 2-investigators,

in 1995, were requested to perform an *in vitro* susceptibility study to assess the *in vitro* effectiveness of trimethoprim (TMP) against *Streptococcus pneumoniae* and *Haemophilus influenzae*, to develop *in vitro* interpretive criteria for testing of the 2-aforementioned microorganisms to trimethoprim, and to reassess the current criteria for T/S. The following is a summary of the *in vitro* susceptibility study:

Study Title:
"Susceptibility of *Haemophilus influenzae* and *Streptococcus pneumoniae* to Trimethoprim and Interpretive Criteria for Trimethoprim Susceptibility Tests with *Haemophilus influenzae* and *Streptococcus pneumoniae*." (Final Report)

Materials and Methods

1. Bacterial Isolates:

Streptococcus pneumoniae:

The study consisted of 234 isolates of *Streptococcus pneumoniae* which were tested. This total included 34 penicillin-resistant strains (MIC ≥ 2.0 μg/mL), 68 penicillin-intermediate strains (MIC = 0.125 to 1.0 μg/mL), and 132 penicillin-susceptible strains (MIC ≤ 0.06 μg/mL). Twenty-seven (27)strains isolated from patients enrolled in recent clinical trials of trimethoprim were included in the total.

Haemophilus influenzae:

The study also consisted of 228 isolates of *Haemophilus influenzae* which were tested. The total included 90 β-lactamase-positive strains and 138 β-lactamase-negative strains [of which 20 were ampicillin-resistant (MIC ≥ 2.0 μg/mL)]. Twenty-three (23) isolates from patients enrolled in recent clinical trimethoprim trials were included in the total.

2. Quality Control Strains:

The following 2-quality control strains from the American Type Culture Collection (ATCC) were used in the study:

Streptococcus pneumoniae ATCC 49619; and
Haemophilus influenzae ATCC 49247

3. Antimicrobial Agents:

Ascent Pharmaceuticals, Billerica, MA., provided the trimethoprim reagent powder.
, provided the sulfamethoxazole powder. For the disk diffusion studies, commercial 5 μg trimethoprim disks and 1.25/23.75 T/S μg were used.

4. Susceptibility Testing:

The susceptibility methods used were according to the National Committee for Clinical Laboratory Standards (NCCLS) for the broth microdilution (MICs), NCCLS M7-A3 Document, and the disk diffusion (zone diameters), NCCLS M2-A5 Document, respectively.

a. *Haemophilus influenzae*

For testing *H. influenzae*, *Haemophilus* Test Medium was used in both (broth microdilution and disk diffusion) methods. In addition, for the microdilution testing 0.2 U/mL thymidine phosphorylase was added to the medium.

b. *Streptococcus pneumoniae*

For testing *S. pneumoniae*, Mueller-Hinton supplemented with 2 to 3% lysed horse blood was used in the microdilution method. For the disk diffusion method sheep blood Mueller-Hinton agar was used.

[Note: There were preliminary trial comparisons of zones of inhibition on the agar with sheep blood to those with the horse blood. The results showed that with horse blood, the zones were clearer and easier to read. However, using sheep blood, those plates really did not present any serious difficulties.]

5. Acceptable Error Rates:[26]

Very Major Errors (= false susceptibility) < 1.5%
Major Errors (= false resistance) < 3%

6. Drug Concentrations:

For both microorganisms, *H. influenzae* and *S. pneumoniae*, the concentration of drugs tested were serial 2-fold dilutions with the following ranges:

Trimethoprim:	16 to 0.008 μg/mL;
Sulfamethoxazole/Trimethoprim:	16/304 to 0.008/0.15 μg/mL; &
Sulfamethoxazole:	304 to 0.15 μg/mL

Results and Discussion

The investigators provided the line listings on the MICs and zone diameters for each drug in Vol. 2, Appendix A, on *Haemophilus influenzae*, pages 02-349 to 02-356, and *Streptococcus pneumoniae*, pages 02-357 to 02-364. The data are summarized as cumulative percent (%) inhibited by increasing concentrations of each drug (Vol. 2, Appendix B, Cum % Inhibited - MIC 50 & MIC 90, *Haemophilus influenzae*, on pages 02-365 to 02-368, and *Streptococcus pneumoniae*, on pages 02-369 to 02-372.

a. *Haemophilus influenzae*

202 out of 228 (= 89%) isolates tested had TMP MICs of ≤ 0.25 μg/mL. These results correlated well with the 89% susceptible to T/S (≤ 0.25 μg/mL). 95% TMP MICs were within 1-twofold concentration of the TMP component in the T/S drug combination. Only a small number of isolates (= 5%) showed a fourfold less susceptibility to TMP alone. Most of the strains were resistant to sulfamethoxazole alone. Any activity of the T/S combination mainly came from the TMP component.

The investigators provided scattergrams and regression statistics correlating the results of the broth microdilution and the disk diffusion tests for both the TMP and T/S drug products against *H. influenzae*. These are shown in Vol. 2, Figure 1, "*H. influenzae* - MICs vs. Zone Diameter for Trimethoprim", on page 02-336, and Vol. 2, Figure 2, "*H. influenzae* - MICs vs. Zone Diameter for Trimethoprim/Sulfamethoxazole", on page 02-337, respectively.

For both drugs, TMP and T/S, the NCCLS M100-S5, M7-A3, Table 2A., Vol. 14, No. 16, 1994, recommended breakpoints for T/S vs. *Haemophilus* species were applied: Susceptible = MIC ≤ 0.5 μg/mL and Resistant = MIC ≥ 4.0 μg/mL. [Note: Also NCCLS, M100-S7, M7-A4, Table 2A., Vol. 17, No. 2, 1997: Susceptible = MIC ≤ 0.5 μg/mL. and Resistant = MIC ≥ 4.0 μg/mL.]

For the 2 drugs, the breakpoints effectively separated the resistant from the susceptible isolates. With the 2-disks, there were neither major errors (false resistance) or very major errors (false susceptible). The TMP disk produced 4 (= 1.8%) minor errors (intermediate) and the T/S disk produced 7 (= 3.1%) minor errors. For susceptibility testing purposes when testing *H. influenzae*, comparing TMP MICs with T/S zone diameters, and vice versa, demonstrated that with these isolates the 2 drugs are interchangeable. This can be seen in the provided scattergrams: Vol. 2, Figure 3, "*H. influenzae* - Trimethoprim MICs vs. T/S Zone Diameters", on page 02-338; Vol. 2, Figure 4, "*H. influenzae* - T/S MICs vs Trimethoprim Zone Diameters", on page 02-339; Vol. 2, Figure 5, "*H. influenzae* - Trimethoprim MICs vs. T/S MICs", on page 02-340; and Vol. 2, Figure 6, "*H. influenzae* - Trimethoprim Zone Diameters vs. T/S Zone Diameters", on page 02-341, respectively. There were no major or very major errors in the comparisons.

There was no difference in the TMP MICs between the β-lactamase-positive (geometric mean MIC = 0.06 μg/mL) and the β-lactamase-negative ampicillin-susceptible (geometric mean MIC = 0.05 μg/mL) isolates. However, the TMP MICs for β-lactamase-negative ampicillin-resistant isolates were 20-fold higher. The geometric mean MIC = 1.2 μg/mL.

b. *Streptococcus pneumoniae*

The investigators also provided scattergrams and regression statistics which correlated the broth microdilution and disk diffusion test results with trimethoprim (TMP) and trimethoprim/sulfamethoxazole (T/S) against *S. pneumoniae*. These are provided in Vol. 2, Figure 7, "*S. pneumoniae* - MICs vs. Zone Diameters for Trimethoprim", on page 02-342, and Vol.2, Figure 8, "*S. pneumoniae* - MICs vs. Zone Diameters for Trimethoprim/Sulfamethoxazole", on page 02-343, respectively.

As previously against *H. influenzae*, for both drugs, TMP and T/S, the NCCLS M100-S5, M7-A3, Table 2C., Vol. 14, No. 16, 1994, recommended breakpoints for T/S vs. *S. pneumoniae* were applied: Susceptible = MIC ≤ 0.5 μg/mL and Resistant = MIC ≥ 4 μg/mL. [Note: Also NCCLS, M100-S7, M7-A4, Table 2C., Vol. 17, No. 2, 1997: Susceptible = MIC ≤ 0.5 μg/mL. and Resistant = MIC ≥ 4.0 μg/mL.]

For T/S the data yielded the following results: no very major errors; 1 (0.4%) major error; and 29 (12.4%) minor errors. The 29 (12.4%) minor errors were nearly all intermediate MICs which correlated with resistant zone diameters. Using these same breakpoints for TMP the data yielded the following results: 2 (0.9%) very major errors (false susceptibility); 5 (2.1%) major errors (false resistant); and 106 (45.3%) minor errors (intermediate). Again, the 106 (45.3%) minor errors were nearly all intermediate MICs which also correlated with resistant zone diameters. In Vol. 2, Figure 9, "*S. pneumoniae* - Trimethoprim MICs vs. Zone Diameters" (using H. influenzae Zone Diameter Breakpoints), on page 02-344, the results show the total error rate for TMP tests would be reduced as follows: Total error rate reduced from 48.3% down to 29.9% with no minor errors . However, there were 8 (3.4%) very major errors (= 7.5% of resistant isolates). The data also show that the cross-correlation between T/S and TMP MICs and zone diameters give high discrepancy rates (Vol. 2 - *S. pneumoniae*: Figure 10, "TMP MICs vs. T/S Zone Diameters"; Figure 11, "T/S MICs vs. TMP Zone Diameters"; Figure 12, "TMP MICs vs. T/S MICs"; and Figure 13, "TMP Zone Diameters vs. T/S Diameters", on pages 02-345 to 02-348). The results also show that the TMP MICs cluster in or near the intermediate category. The investigators believe that there would be a cleaner separation of susceptible and resistant isolates, if the susceptible MIC breakpoint = MIC ≤ 2.0 μg/mL and the intermediate MIC breakpoint = MIC = 4.0 μg/mL (as with other microorganisms listed in the NCCLS M100-S5, Table 2).

The investigators provided the following correlation coefficient (r) results: When testing TMP susceptibility of pneumococci by the 2-methods, the correlation coefficient is very poor (r = 0.32) compared to that of T/S (r = 0.88). Therefore, at this time, there are no recommendations for disk testing against *S. pneumoniae*.

Pages 31-41

REDACTED

CONFIDENTIAL

COMMERCIAL

INFORMATION

PACKAGE INSERT

ISOLATES APPROVED

The following indication and microorganisms are recommended for approval on this NDA 20-651 submission and are to be added to the approved labeling:

1. For Acute Otitis Media:

Haemophilus influenzae (excluding beta-lactamase negative, ampicillin resistant strains)

Streptococcus pneumoniae (penicillin-susceptible strains)

INTERPRETATIVE CRITERIA ESTABLISHED

See the following **Susceptibility Tests** subsection and the aforementioned pages 40 and 41 in this Review.

The **Microbiology** subsection and the **Susceptibility Tests** subsection should be revised in accordance with the January 26, 1993, letter to all NDA Holders from the Division of Anti-infective Drug Products, as well as recent discussions within the Division and between Ascent (FAX dated 3/14/97). Also refer to Ascent's original PRIMSOL® drug product and labeling, approved on 6/23/95). The microbiology portion of the labeling should read as follows:

CLINICAL PHARMACOLOGY (Microbiology subsection and Susceptibility Tests subsection:

Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. Thus, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

Trimethoprim has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Staphylococcus species (coagulase-negative strains, including *S. saprophyticus*))
Streptococcus pneumoniae *(penicillin-susceptible strains)*

Aerobic gram-negative microorganisms

Enterobacter species
Escherichia coli
Haemophilus influenzae (excluding beta-lactamase negative, ampicillin resistant strains)
Klebsiella pneumoniae
Proteus mirabilis

NOTE: *Moraxella catarrhalis* isolates were found consistently resistant to trimethoprim.

Susceptibility Tests

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trimethoprim powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms isolated from urinary tract infections:

MIC (ug/mL)	Interpretation
≤ 8	Susceptible (S)
≥ 16	Resistant (R)

When testing *Haemophilus influenzae*[a]

MIC (ug/mL)	Interpretation
≤ 0.5	Susceptible (S)
1-2	Intermediate (I)
≥ 4	Resistant (R)

When testing *Streptococcus pneumoniae*[b]

MIC (ug/mL)	Interpretation
≤ 2	Susceptible (S)
≥ 4	Resistant (R)

a. Interpretative criteria applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1]

b. Interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trimethoprim[a] powder should provide the following MIC values:

Microorganism		MIC (µg/mL)
Escherichia coli	ATCC 25922	0.5-2
Haemophilus influenzae[b]	ATCC 49247	0.06-0.5
Staphylococcus aureus	ATCC 29213	1-4
Streptococcus pneumoniae[c]	ATCC 49619	1-4

a. Trimethoprim very medium-dependent.

b. Range applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1]

c. Range applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg trimethoprim to test the susceptibility of microorganisms to trimethoprim.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg trimethoprim[a] disk should be interpreted according to the following criteria:

For testing aerobic microorganisms isolated from urinary tract infections:

Zone diameter (mm)	Interpretation
≥ 16	Susceptible (S)
11-15	Intermediate (I)
≤ 10	Resistant (R)

When testing *Haemophilus influenzae*[b]

Zone diameter (mm)	Interpretation
≥ 16	Susceptible (S)
11-15	Intermediate (I)
≤ 10	Resistant (R)

a. Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥ 20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

b. Interpretative criteria applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[2]

Note:

Diffusion techniques are not recommended for determining susceptibility of *Streptococcus pneumoniae* to trimethoprim.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trimethoprim.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg trimethoprim[a] disk should provide the following zone diameters in this laboratory test quality control strain:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	21-28
Haemophilus influenzae[b]	ATCC 49247	27-33
Staphylococcus aureus	ATCC 25923	19-26

a. Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥ 20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

b. Range applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[2]

Note:
Diffusion techniques are not recommended for determining susceptibility of *Streptococcus pneumoniae* to trimethoprim.

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In conclusion, from the clinical microbiology perspective, Ascent Pharmaceuticals, Inc, should be notified that NDA 74-374 is "approvable" for acute otitis media. [See the aforementioned **PACKAGE INSERT** and the corresponding subsections, on pages 42 to 48.]

Harold V. Silver
Clinical Microbiology Reviewer
DAIDP/HFD-520

cc: Orig. NDA 74-374
HFD-520/Division File
HFD-615/MO/MFanning
HFD-615/DLPS/CParise
HFD-650/LGavin
HFD-520/Micro/HVSilver:
12/26/96;3/18/97
HFD-520/TLMO/JSoreth
HFD-520/MO/SMaloney
HFD-520/DOBIV/RHarkins
HFD-520/ProjMgr/BDuvall-Miller
HFD-520/ProjMgr/CDebellas
filename(s): 74374mic.fin
APPROVABLE

Concurrence Only:
HFD-520/ActgDivDir/DFeigal
HFD-520/DepDir/LGavrilovich
HFD-520/TLMicro/ATSheldon
HFD-520/TLMicro/RD init.
by A.T.Sheldon
Final Init. 3/18/97 AS 3/18/97
3/20/97

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074374 /S001, S002

MEDICAL OFFICER REVIEW

MEDICAL OFFICER'S REVIEW
NDA: 74-374
ASCENT PHARMACEUTICALS, INC.
TRIMETHOPRIM HYDROCHLORIDE ORAL SOLUTION
CLINICAL EFFICACY SUPPLEMENT FOR PEDIATRIC PATIENTS

MEDICAL OFFICER'S REVIEW
NDA/ANDA:74-374
TRIMETHOPRIM HYDROCHLORIDE ORAL SOLUTION
CLINICAL EFFICACY SUPPLEMENT FOR PEDIATRIC PATIENTS
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MEDICAL OFFICER'S REVIEW OF NDA 74-374
TRIMETHOPRIM HYDROCHLORIDE ORAL SOLUTION
CLINICAL EFFICACY SUPPLEMENT FOR PEDIATRIC PATIENTS

DATE OF SUBMISSION: January 3, 1996

I. OVERVIEW OF SUPPLEMENT SUBMISSION

APPLICANT: Ascent Pharmaceuticals, Inc
9 Linnell Circle
Billerica, MA. 01821

DRUG:

Generic Name: Trimethoprim hydrochloride (oral solution)

Trade Name: Primsol Solution
(Dye-free, alcohol-free, flavored solution, 25 mg trimethoprim per 5 mL)

Chemical Name: ***Trimethoprim***: 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine

Molecular Formula: ***Trimethoprim***: C14H18N4O3

Molecular Weight: ***Trimethoprim***: 290.32

Route of Administration: Oral

Dosage Form: Primsol (trimethoprim hydrochloride oral solution) is a solution of the synthetic antibacterial trimethoprim in water prepared with the aid of hydrochloric acid. Each 5 mL for oral administration contains trimethoprim hydrochloride equivalent to 25 mg triemthoprim and the inactive ingredients bubble gum flavor, methylparaben, propylparaben, propylene glycol, saccharin sodium, sucrose, water and hydrochloric acid to adjust pH to a range of 3.0-5.0.

Pharmacologic Category: Dihydrofolate reductase inhibitor

Medical Officer's Comments: ***Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. This binding is much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. Thus, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.***

media and nd data submitted from the published literature addressing treatment efficacy of trimethoprim in pediatric respiratory infections and

RELATED IND:

PROPOSED LABELING:

Acute Otitis Media: For the treatment of acute otitis media due to susceptible strains of *Haemophilus influenzae* and *Streptococcus pneumoniae.* Primsol is not indicated for prophylactic or prolonged administration in otitis media at any age.

Medical Officer's Comments: Please refer to the separate section titled "SUMMARY RECOMMENDATIONS AND LABELING GUIDANCE" for a discussion of the medical officer's summary recommendations and labeling guidance.

CHEMISTRY, MANUFACTURING AND CONTROLS:

The reader is referred to the chemistry reviews by Eugene L. Schaefer, Ph.D.

Dr. Schaefer's conclusions and recommendations in his addendum to Chemistry Review #5 state:

"The 24 month stability data and the revised stability specification range are satisfactory. "

Medical Officer's Comments:

Packaging and labeling were deemed satisfactory in Review #1.
Manufacturing and processing, and laboratory controls were deemed satisfactory in Review #2.
The Office of Compliance issued an UNACCEPTABLE status for manufacturer of the drug substance for NDA 74-374. Subsequently, this company's facility The NDA was thus approved without a drug substance manufacturer. Ascent Pharmaceuticals has not manufactured or distributed Primsol Oral Solution since the NDA was approved. Ascent Pharmaceuticals will need to supplement the NDA for approval of a new supplier. The chosen facility will need to be inspected and evaluated.

PHARMACOKINETICS:

Pharmacokinetics

The following information was included by the applicant in this submission:

A review of the literature on trimethoprim reveals that characteristic pharmacokinetic

parameters such as half-life, clearance, and volume of distribution, all vary with age. Excluding newborns, an apparent trend of increasing half-life and volume of distribution, and decreasing clearance, is observed with increasing age, until, by adulthood, these pharmacokinetic parameters are similar to those seen in the newborn.

As shown in Table 1, when compared to children 1-13 years old, newborns exhibit relatively long TMP half-lives (19h in newborns vs. 3.7-6.8h in 1-13 year-olds), large volumes of distribution (2.7 vs 0.86-2.24 L/kg), and slow clearances (1.84 vs. 2.4-4.01 mL/min/kg). Comparing the pharmacokinetic data from newborns [6] to values found in children 1-3 years old [7], furthermore, demonstrates a significant decrease in half-life (19h in newborns to 3.7h in 1-3 year-olds) and volume of distribution (2.4 to 0.86 L/kg), and a significant increase in clearance rate (1.84 to 2.8 mL/min/kg). The percent of the dose recovered in the urine also appears to vary with age (Table 1), though there is not as clear a trend with age as is noted with the pharmacokinetic parameters discussed above.

Other pharmacokinetic parameters, such as C_{max} and T_{max}, do not appear to vary as much with age. Hoppu (1987)[7], for example, following a 3mg/kg dose every 12h for 10 days, observed maximum plasma concentrations of 2.2 μg/mL and 2.3 μg/mL for 1 to 3 year-old and 8 to 10 year-old, respectively. The same dose in adults also resulted in a C_{max} of TMP of 2.3 μg/mL. Similarly, in the same study, the T_{max} was 1.9h in the adults, and ranged on average from 1.7h to 2.3h in the children.

Effect of Subject Age on TMP pharmacokinetics

Subjects	Formulation	Route	TMP Pharmacokinetic Parameters				Reference
			Half-life	Vol. Dist. L/kg	Clearance mL/min/kg	Urine: %Dose Excreted	
N=12, newborns <3d postnatal (mean weight=1600g)	TMP+SMX	IV	1st Dose: 19±1.3h 10.8-27.2h Mult. Dose: 24.6±2.3h	2.7±0.24 1.32-4.10	3.31±0.7mL/min (1.84 mL/min/kg) 1.17-9.17 mL/min		Springer, et. al., 1982 (1)[6]
N=18 children 3 weeks-13 years	TMP+SMX	1hr IV infusion	1st Dose: 5.3h Mult. Dose: 5.2h				Ardati, et. al., 1979 (2)[8]
N=18 children 3mos.-13years	TMP	oral	6.8±1.6h	2.24±0.57	4.01±1.32	@12h: 20% @24h: 34% (Cmax:180mg/L range:10-640)	Rylance, et. al., 1985 (3)[9]
N=9 girls 1-3yr N=9 girls 8-10yr N=12 adults (3 female, 9 male)	TMP	oral	mean (95%CI) 1-3y: 3.7h (3.2-4.1h) 8-10y: 5.4h (4.3-6.5h) Adults: 11.2h (10.2-12.4h)	mean (95%CI) 1-3y: 0.86(0.75-0.96) 8-10y: 1.08(0.93-1.22) Adults: 1.31(1.21-1.40)	CL: mean (95%CI): 1-3y: 2.8(2.4-3.3) 8-10y: 2.4(2.1-2.7) Adults: 1.4(1.3-1.5)	mean (95%CI) 1-3y: @12h 51.7% (33.8-69.7) 8-10y: @12h 39.1 %(29.9-48.3) Adults: @24h 44.6%(39.7-49.5)	Hoppu, 1987 (4)[7]
A: N=4; 2y B: N=3; 4y C: N=5; 6y D: N=5; adults	TMP+SMX	oral	A: 5h B: 2h30m C: 4h D: 10h15m			@24h A: 30±7% B: 49±26% C: 62±10% D: 43±5%	Kremers, et. al., 1973 (5)[10]

TMP=trimethoprim SMX=sulfamethoxazole

BIOEQUIVALENCE:

The reader is referred to Dr. Man M. Kochnar's Bioequivalence review.

His recommendations are summarized below:

"1. The fasting bioequivalence study conducted by Ascent on its Trimethoprim (Primstat [now Primsol]) syrup, 25 mg/5 mL lot # 3EX01A28, comparing it to Trimpex Tablets 100 mg, lot # 0433 manufactured by Roche, has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Ascent's Trimethoprim Syrup 25 mg/5 mL is bioavailable to the extent of Trimpex Tablets, 100 mg (Reference Product), manufactured by Roche."

"2. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence study, and therefore, the application is approvable."

Medical Officer's Comments: The applicant reports that two bioequivalence studies were performed for Ascent Pharmaceuticals with trimethoprim hydrochloride oral solution in adult volunteers. The first was a pilot study, while the second definitive study was the basis for approval of the original NDA application. The company did not conduct any bioavailability studies in children.

MICROBIOLOGY:

The reader is referred to the Dr. Harold Silver's Microbiology review for full evaluation and recommendations.

Medical Officer's Comments: In vitro studies have demonstrated that trimethoprim is active against a wide range of pathogenic bacteria including those that commonly cause infections of the urinary and respiratory tracts. The spectrum of antibacterial activity of trimethoprim includes the common urinary tract pathogens: Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter species, Staphylococcus saprophyticus, and coagulase-negative Staphylococcus species. Trimethoprim is not active against Pseudomonas aeruginosa. The applicant states that the usual spectrum of antimicrobial activity of trimethoprim also includes the following bacterial pathogens isolated from middle ear exudate: Haemophilus influenzae, both beta-lactamase positive and negative strains, and Streptococcus pneumoniae. The applicant further states that trimethoprim has been shown to be active against the following organisms, both in vitro and in clinical infections:

Gram-positive Organisms

Streptococcus pneumoniae
Staphylococcus species (coagulase-negative)

Gram-negative Organisms

Escherichia coli
Haemophilus influenzae (beta-lactamase positive and negative)
Proteus mirabilis
Klebsiella pneumoniae
Enterobacter species

The applicant has reported in this submission that the conducted two in vitro microbiology studies with trimethoprim (TMP) and trimethoprim/sulfamethoxazole (TMP+SMX) against H. influenzae and S. pneumoniae and prepared a detailed report for each. The purpose of these studies was fourfold: 1) to assess the in vitro effectiveness of TMP against S. pneumoniae and H. influenzae 2) to develop in vitro interpretive criteria for testing susceptibility of these two species to TMP 3) to define quality control parameters for susceptibility testing of H. influenzae and S. pneumoniae to TMP and 4) to correlate the in vitro susceptibility data with in vivo clinical response data from the otitis media trial in children (T-OM-01). Although the medical officer did not find the full report of the Institute in this submission, the applicant presented the following data:

The recommends the following quality control range for TMP:

H. influenzae ATCC 49247: *MIC range = 0.06 to 0.5 mcg/mL*
Zone range = 27 to 33 mm

S. pneumoniae ATCC 49619: *MIC range = 1.0 to 4.0 mcg/mL*
Zone range = No recommendation

The Institute recommended the following breakpoints for testing trimethoprim:

Species and Category	*MIC*	*Zone Diameter*
H. influenzae		
Susceptible	*≤2.0 mcg/mL*	*≥16 mm*
Intermediate	—	*11-15 mm*
Resistant	*≥4.0 mcg/mL*	*≤10 mm*
S. pneumoniae		
Susceptible	*≤2.0 mcg/mL*	*No recommendation*
Resistant	*≥4.0 mcg/mL*	*No recommendation*

APPEARS THIS WAY
ON ORIGINAL

clinical trials undertaken for this submission:

" Busby and Hithchings[1] introduced the use of trimethoprim (TMP) as a potentiator of sulfonamide activity in 1968, and the specific combination of trimethoprim and sulfamethoxazole (SMX) is marketed as a suspension. The combination of TMP and SMX was based, in part, upon the observed synergy in the laboratory with regard to bacteriostasis and bacteriocidal activity. Ekstrom and coworkers demonstrated the synergism of TMP and sulfonamides for a variety of ratios of TMP to sulfonamides ranging from 1:10 to 1:40. Another rationale for combining TMP with sulfonamides was the perceived potential to minimize the emergence of organisms resistant to either compound. Both of theses assumptions for combining TMP with SMX, however, have come under closer scrutiny over the past two decades, and have not always held up upon clinical evaluation. The potential synergism of TMP and SMX, for example, is nonexistent in the urine where, due to the metabolism of SMX, the 1:20 ratio of TMP:SMX found in the blood falls to 1:1. This has led a number of investigators to conclude that the inhibitory power in urine from Cotrimoxazole, and other TMP-sulfonamide combinations is entirely due to TMP. Similarly, investigations of development of secondary resistance due to the use of TMP alone as opposed to the use of TMP with SMX, have failed to demonstrate any increase in the emergence of resistant bacterial strains due to the use of TMP alone."

"While the combination of TMP+SMX, therefore, has proven extremely useful in the chemotherapy of many infectious diseases, and has been considered ideal for the treatment of urinary and respiratory tract infections, there is evidence to support the use, instead, of trimethoprim alone.[2]"

Medical Officer's Comments: The applicant also cites the claim for less frequent adverse events (including Stevens Johnson syndrome) associated with the administration of TMP alone when compared with TMP+SMX as a rationale for the conduct of the pediatric clinical trials.

The use of trimethoprim (TMP) monotherapy is approved in the United States for treating uncomplicated urinary tract infections in patients 12 years or older.

Ascent chose to conduct clinical trials for acute otitis media indications in children 6 months to 12 years of age. Two comparative trials were conducted as multicenter, randomized, parallel group studies, comparing the safety and efficacy of TMP monotherapy with trimethoprom plus sulfamethoxazole combination therapy in OM

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[1]Bushby S, Hitchings G. "Trimethoprim, a sulphonamide potentiator." Brit J Pharmacol, 33:72(1968).

[2] Please refer to applicant's submission, Volume 1, pp.01-041and 01-042 for complete references for applicant's statements.

infections in pediatric patients. A third multicenter , noncomparative trial in acute otitis media was performed utilizing tympanocentesis with collection and culturing of the middle ear fluid to determine pathogens and define bacteriologic response to monotherapy. A total of 521 pediatric patients were enrolled in the three clinical trials. The next table summarizes and describes the three clinical trials:

BACKGROUND/OVERVIEW OF CLINICAL INVESTIGATIONS

SUMMARY OF CLINICAL TRIALS

PROTOCOL	INDICATION	NO. OF PATIENTS	AGE RANGE	DESIGN	VISITS	BASELINE CULTURE	PRIMARY EFFICACY VARIABLES
T-OM-02	AOM	TMP: 133 TMP+SMX:129	6 mo. - 12 yr.	Comparative	Days 4, 15, 30	None	Overall Clinical Outcome
T-OM-01	AOM	TMP: 120	6 mo. - 12 yr.	Open - Label Non-comparative	Days 4, 15, 30	Middle Ear Effusion	Bacteriological Response Overall Clinical Outcome

DOSAGES:

TMP Group = TMP 10 mg/kg/day (maximum 400 mg/day) in 2 divided doses x 10 days.

TMP+SMX Group = TMP 8 mg/kg/day + SMX 40 mg/kg/day (maximum TMP 320 mg/day + SMX 1600 mg/day) in 2 divided doses x10 days.

II. REVIEW OF CLINICAL STUDIES
INDICATION: ACUTE OTITIS MEDIA
Protocol: T-OM-02

Title: Randomized Trial Comparing Primsol Solution (Trimethoprim) and Septra Pediatric Suspension (A Combination of Trimethoprim and Sulfamethoxazole) in Pediatric Patients with Acute Otitis Media.

Study Dates: January 14, 1994-October 17, 1994.

Objective: To compare the safety and clinical efficacy of Primsol (R) Solution (trimethoprim 10 mg/kg/day for 10 days) with Septra (R) Pediatric Suspension (trimethoprim 8 mg/kg/day and sulfamethoxazole 40 mg/kg/day for 10 days) in the treatment of acute otitis media in pediatric patients.

A. STUDY SUMMARY

Study Design: Randomized, investigator-blinded, comparative multicenter study of parallel design.

Method of Patient Assignment: Sealed randomization codes were included with the study drug shipments. Patients who met the inclusion and exclusion criteria for the study were assigned numbers in sequential order. A separate envelope was provided for each patient.

Inclusion Criteria:

Patients meeting the following criteria were included in the study:

1. Age range: 6 months to 12 years.
2. Males or females.
3. Outpatients (not hospitalized).
4. ***Diagnosis of acute otitis media*** was made as follows:
   - by the presence of one or more of the following clinical symptoms: pain in the affected ear, lethargy, irritability, or fever.
   - by examination of the tympanic membrane and the presence of one or more of the following signs: dilation of the blood vessels on the malleus and at the annulus, diffuse dullness, erythema, loss of normal landmarks, or bulging of the drum.
   - by evidence of middle ear effusion in the affected ear documented by pneumatic otoscopy and/or tympanometry.

Exclusion Criteria:

Patients meeting any of the following criteria were to be excluded from study entry:

1. History of allergy to trimethoprim and/or sulfamethoxazole.
2. Chronic otits media (5 or more episodes, including the current episode, in the past 12 months).
3. Suppurative otitis media.
4. Intercurrent use of antihistamines or decongestants.
5. Known clinical history or signs (in the judgement of the clinical investigator) of significant renal impairment (>50% elevation above the upper limit of normal in serum creatinine values), hepatic dysfunction (>50% increase above the upper limit of normal in serum ALT,AST,and/or bilirubin), or patients with hematologic abnormality or cardiovascular disease requiring medical intervention.
6. Patients with a history of glucose-6-phosphate dehydrogenase deficiency, folate deficiency, or megaloblastic anemia.
7. Patients with known or suspected severe allergies or bronchial asthma.
8. Treatment with other antimicrobials within 14 days prior to entry or during this study.
9. History of neutropenia or opportunistic infections.
10. Malabsorption syndrome.
11. Anticonvulsant therapy with phenytoin.
12 Presence or evidence of another significant underlying disease which precludes evaluation of response to therapy, including states of immunosuppression.
13. Patients with craniofacial defects.
14. Previous otic surgery.
15. Treatment with another investigational drug within 30 days prior to study entry or during this study.
16. Positive urine pregnancy test in females of childbearing potential.
17. Parents/Guardians of patients unable or unwilling to sign informed consent form.

Study Drug, Dosage, and Duration of Therapy:

The recommeded dose of Primsol Solution (25 mg trimethoprim/5 mL) was 10 mg/kg/day (maximum dosage=400 mg per day), given in two divided doses every 12 hours for 10 days. The timing of dosing in relation to meals was not considered important to the design of the trial, or the absorption of the antimicrobial.

The recommended dose of Septra (40 mg trimethoprim/200 mg sulfamethoxazole/5 mL) was 8 mg/kg/day trimethoprim and 40 mg/kg/day sulfamethoxazole (maximum dosage=320 mg trimethoprim and 1600 mg sulfamethoxazole per day), given in two divided doses every 12 hours for 10 days.

Assessment of Compliance:

The first dose of test medication was administered by the dosing administrator following enrollment into the study. At the end of the treatment period, all study medication bottles were required to be returned to the study site. Assessment of patient compliance to the dosing schedule was made by measuring the volume of returned medication.

Concomitant Therapy:

All medications taken within 30 days prior to entry into the study were recorded. All medications that were continued during the study period were recorded on the case report form (CRF). Antihistamines, decongestants, and antimicrobial agents were not to be administered during the study period. Antipyretic agents were to be administered at the discretion of the parent/guardian or physician.

Schedule of Assessments:
The following figure provides a study flow chart showing timing of visits and measurements recorded at each visit during the protocol:

	Visit 1 (Screen) Day 1	Visit 2 Day 4	Visit 3 Day 13-17	Visit 4 [a] Day 27-33
Inclusion/Exclusion Criteria	X			
Medical History	X			
Physical Examination	X	(brief)	(brief)	(brief)
Acute Otitis Media Symptoms and Signs Assessment	X	X	X	X
Assessment of Patient Response		X	X	X
Tympanocentesis and Middle Ear Effusion Culture		X [b]	X [b]	X [b]
Assess Adverse Events		X	X	X
Record Concomitant Medications	X	X	X	X
Serum Chemistry, CBC	X			X
Drug Accountability	X	X	X	
Termination Sheet				X

a. If the patient is withdrawn from this study prior to visit 4, these procedures should be performed.
b. If warranted.

Study Assessments:

Clinical Assessments:
Clinical Evaluations, Visits 1-4: At each visit, a physical examination was performed, including pneumatic otoscopy and/or tympanometry to assess signs and symptoms of acute otitis media. All important characteristics of the tympanic membranes including color, transparency, luster, mobility, and vascularity were evaluated. Presence or absence of middle ear effusion was documented.
Clinical Response: See EVALUABILITY CRITERIA AND EFFICACY EVALUATIONS Section to follow.

Medical Officer's Comments: Tympanocentesis and middle ear effusion cultures were not a requirement of enrollment for participation in this clinical trial. However, as can be seen clearly from the study flow chart for protocol T-OM-02, these procedures were to be performed, "if warranted". After Ascent's discussions with the FDA, it was agreed that tympanocentesis and cultures of middle ear fluid would be incorporated into the protocol for all patients deemed clinical failures. The Medical Officer can find no evidence that these procedures were performed for patients evaluated as clinical failures, and no reports or discussion of culture results in the present submission. This oversight is unfortunate, and makes evaluation of the cause of clinical failures difficult. Tympanocentesis in patients judged to be therapeutic failures is specifically encouraged to document potential specific bacterial pathogens not adequately treated in the trial.

Safety Assessments (Adverse Events and Laboratory Evaluation):
Adverse Events: Parents/Guardians were instructed to report any adverse events to the investigator. At each clinical assessment, all new or continuing adverse events, as well as worsening baseline conditions, were recorded, regardless of severity and relationship to study drug. All serious or unexpected adverse events were to be reported immediately by telephone to Oxford Research International Corporation and to the applicant, and a written report was required to be submitted to the medical monitor within 24 hours. All serious adverse events were to be followed through resolution.

Laboratory Evaluation: Laboratory tests, including complete blood counts, and serum chemistries including serum creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin, and blood urea nitrogen were to be obtained at the initial and last follow-up visits, or more often if considered medically indicated by the clinical investigator.

B. EVALUABILITY CRITERIA AND EFFICACY EVALUATIONS

Applicant Criteria for Evaluable Patients:

The following patient populations were included in the efficacy analyses:

Intent-to-Treat Patients

All patients randomized into the study with the exception of 3 patients who did not return after the initial visit.

Efficacy Evaluable Patients

All patients who met the inclusion/exclusion criteria, and met the following rules:

1. No antihistamine/decongestant taken ≥ 3 consecutive days.
2. No antimicrobial therapy taken within 14 days prior to entry (as per protocol).
3. No history of chronic otitis media.
4. Patient dosed ≥7 days.
5. Patient had a Day 30 (Visit 4) evaluation.
6. No visit out of range. The window allocated for each visit was expanded from the protocol timing of visits as follows:

Visit 2=2-6 days
Visit 3=12-18 days
Visit 4=25 days or more

7. No major protocol violation.

Applicant Assessment of Clinical Response:

The investigator made an assessment of **Clinical Response** to treatment on Visits 2, 3, and 4, (respectively) according to the following criteria:

Visit 2 Evaluation (Day 4):

Complete Response : Complete resolution of baseline signs and symptoms with or without middle ear effusion. No new significant signs or symptoms of acute otitis media.

Partial Response: Partial resolution of baseline signs and symptoms with or without middle ear effusion No new significant signs or symptoms of acute otitis media.

No Response: No resolution of baseline signs and symptoms. Appearance of significant new signs and symptoms of acute otitis media.

Visit 3 Evaluation (Day 15):

Complete Response: See Visit 2 definition.

Partial Response: See Visit 2 definition.

Relapse: Complete Response or Partial Response at Visit 2. Reappearance or increase of significant signs and symptoms of acute otitis media.

Visit 4 Evaluation (Day 30):

Complete Response: See Visit 2 definition.

Partial Response: See Visit 2 definition.

Recurrence: Reappearance of significant signs and symptoms of acute otitis media at Visit 4, after demonstration of Complete Response at Visit 3.

The applicant analysed **Overall Clinical Response** at Visit 3 and Visit 4 as follows:

Early Cure =Complete Response at Visit 2, Complete Response at Visit 3, no Relapse, no Recurrence.

Late Cure=Partial Response at Visit 2, Complete Response at Visit 3, no Relapse, no Recurrence.

Improvement=Partial Response at Visit 2 or Visit 3, with no Relapse, no Recurrence.

Failure=No Response at Visit 2.

Relapse=Complete or Partial Response at Visit 2 with reappearance or increase in significant signs and symptoms at Visit 3.

Recurrence=Complete Response at Visit 3 with reappearance of significant signs and symptoms of acute otitis media at Visit 4..

Medical Officer's Comments: Note: In the Intent-to-Treat Analysis, those patients missing Visit 4 evaluation and showing only improvement through Visit 3 were considered failures. Patients with an early or late cure missing the Visit 4 evaluation were considered cures in the Intent-to-Treat analysis.

The applicant also made an assessment of **Overall Clinical Response at Endpoint** as

successful (Early Cure, Late Cure, or Improvement)
or
unsuccessful (Failure, Relapse, or Recurrence) at endpoint (last evaluation).

Medical Officer's Comments: The medical officer agreed with the applicant's criteria for the Intent-To-Treat patient analysis. The medical officer also agreed with the efficacy evaluability rules 1-3 and 7 for the efficacy evaluable patient population. However, in order to include the largest number of patients in the evaluable population, the medical officer used the following rules for required duration of therapy and timing of evaluations of clinical efficacy.

Medical Officer Criteria for Evaluable Patients

Efficacy Evaluable Patients

All patients who met the inclusion /exclusion criteria, and met the following rules:

1. No antihistamine/decongestant taken ≥ 3 consecutive days.
2. No antimicrobial therapy taken within 14 days prior to entry (as per protocol).
3. No history of chronic otitis media.
***4. Patient dosed ≥72 hours*
***5. Patient had one evaluation at least 10 days after discontinuation of antimicrobial therapy.*
***6. Patient was not considered not evaluable because a visit was out of range. The Medical Officer required the patient to have an initial evaluation, and one follow-up evaluation at least 10 days after discontinuation of antimicrobial therapy.*
7. No major protocol violation.

*** These evaluability criteria differ from the applicant's evaluability criteria.*

Medical Officer Assessment of Clinical Response:

The Medical Officer agreed with the applicant's assessment for clinical response for Intent-to-Treat and efficacy evaluable patient analyses. For efficacy evaluable patients, the medical officer evaluated clinical response at the last study visit in the same manner as the applicant for overall clinical response at endpoint [success (successful) or failure (unsuccessful)].

C. STUDY DESIGN, PATIENT EVALUATION, AND EFFICACY ANALYSES

Study Design and Evaluability

The applicant conducted this study protocol with patients enrolled by investigators at 11 centers in the United States. Overall, 262 patients were enrolled.

The next table sumarizes the number of patients enrolled by center:

NUMBER OF PATIENTS ENROLLED BY CENTER
Protocol T-OM-02

Principal Investigator/Center Number/ State	TMP n=133	TMP+SMX n=129	Total n=262
Winner/21/Georgia	2	3	5
Kassman/22/North Carolina	10	8	18
Carnaggio/23/Alabama	9	8	17
Hofer/24/Illinois	24	23	47
Bader/25/Washington	1	1	2
Gabrielson/26/Utah	18	18	36
McCarty/27/California	23	24	47
Kirstein/28/Utah	9	8	17
Smucker/29/Ohio	6	5	11
DeAbate/30/Louisiana	30	30	60
Guthrie/31/Utah	1	1	2

The next table summarizes the number of patients in the Intent-to-Treat (ITT) and efficacy evaluable and not evaluable patient populations as rendered by the applicant and medical officer for each treatment regimen:

INTENT TO TREAT (ITT) AND EVALUABLE AND NOT EVALUABLE PATIENTS (PER APPLICANT AND MEDICAL OFFICER) BY TREATMENT REGIMEN

	TMP	TMP+SMX	TOTAL
No. of **ITT Patients**	130*	129	259
No. of **Evaluable Patients per Applicant**	115	111	226
No. of **Not Evaluable Patients per Applicant**	15	18	33
No. of **Evaluable Patients per Medical Officer**	122	117	239
No. of **Not Evaluable Patients per Medical Officer**	8	12	20

* Three patients were randomized to treatment with TMP, but had no post-baseline efficacy assessment, and were excluded from the ITT analysis

The next table summarizes the applicant's reasons for excluding patients from the efficacy analysis:

Reasons for Exclusion from Efficacy Analysis

Reason	TMP n=15	TMP+SMX n=18	TOTAL n=33
Visit out of range	9	7	16
Chronic otitis media	2	2	4
Antihistamine/decongestant	2	2	4
Antibiotic use	0	2	2
Visit 4 missing	0	2	2
Dosed <7 days	2	1	3
Other inclusion/exclusion criteria	0	2	2

Medical Officer's Comments: As outlined previously, the medical officer's criteria for efficacy evaluability differed slightly from the applicant's criteria. These differences in evaluability criteria led to differences in categorizing patients as evaluable and not evaluable. Additionally, after the medical officer reviewed the investigator's clinical assessments for each visit, the medical officer differed in assignment of clinical response for several patients. The next table summarizes the differences in evaluability assessment between the applicant and the medical officer:

Differences in Evaluability Assessment between Applicant and Medical Officer

Center/Patient Number/Regimen	Applicant Assessment	Medical Officer Assessment
21/001/TMP+SMX	Not evaluable	Failure
21/002 /TMP+SMX	Improvement	Failure
22/004/TMP+SMX	Failure	Success
22/014/TMP+SMX	Not evaluable	Success
22/016/TMP	Not evaluable	Success
22/018/TMP	Not evaluable	Success
23/003/TMP	Not evaluable	Success
23/010/TMP+SMX	Failure	Not evaluable
24/018/TMP	Improvement	Not evaluable
24/024/TMP	Cure	Not evaluable
24/026/TMP	Not evaluable	Success
24/046/TMP+SMX	Not evaluable	Success
26/006/TMP+SMX	Not evaluable	Failure
26/011/TMP	Not evaluable	Success
26/033/TMP	Not evaluable	Success
27/028/TMP	Not evaluable	Success
29/006/TMP	Not evaluable	Success
29/007/TMP+SMX	Not evaluable	Success
29/011/TMP	Not evaluable	Success
30/039/TMP+SMX	Not evaluable	Success
31/001/TMP+SMX	Not evaluable	Success

Patient Enrollment by Investigation Site

The following table presents the the number of patients in the Intent-To-Treat (ITT) and efficacy evaluable patient populations [as rendered by the Applicant (A) and the Medical Officer (MO)] by investigation site:

INTENT TO TREAT AND EVALUABLE PATIENTS BY INVESTIGATION SITE (AS RENDERED BY APPLICANT AND MEDICAL OFFICER) BY TREATMENT REGIMEN

Investigator/Center	TMP			TMP+SMX			Total		
	ITT	A	MO	ITT	A	MO	ITT	A	MO
Winner/21	2	1	1	3	1	2	5	2	3
Kassman/22	10	8	10	8	7	8	18	15	18
Carnaggio/23	9	7	8	8	7	6	17	14	14
Hofer/24	24	21	20	23	21	22	47	42	42
Bader/25	1	1	1	1	0	0	2	1	1
Gabrielson/26	18	16	18	18	14	15	36	30	33
McCarty/27	23	21	22	24	24	24	47	45	46
Kirstein/28	9	9	9	8	7	7	17	16	16
Smucker/29	6	3	5	5	3	4	11	6	9
DeAbate/30	30	27	27	30	27	28	60	54	55
Guthrie/31	1	1	1	1	0	1	2	1	2
Total	133	115	122	129	111	117	262	226	239

ITT=Intent-To-Treat
A=Applicant
MO=Medical Officer

Medical Officer's Comments: ***No center enrolled greater than 50% of the ITT or efficacy evaluable populations.***

Demographic and Clinical Characteristics of Intent-To-Treat and Efficacy Evaluable Patients

The following table compares the demographics of the ITT and the efficacy evaluable patients as rendered by both the applicant (A) and the medical officer (MO):

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF INTENT-TO-TREAT AND EFFICACY EVALUABLE PATIENTS

Characteristic	ITT		Applicant Evaluable		Medical Officer Evaluable	
	TMP	TMP+SMX	TMP	TMP+SMX	TMP	TMP+SMX
Total Patients	130	129	115	111	122	117
Sex (n,%)						
Male	64(49)	67(52)	58(50)	57(51)	62(51)	59(50)
Female	66(51)	62(48)	57(50)	54(49)	60(49)	58(50)
Age						
(mean,*years*)	3.0	3.7	2.9	3.7	3.17	3.8
(range)	(0.5-12)	(0.5-12)	(0.5-12)	(0.5-12)	(0.5-12)	(0.5-12)
(mean,*months*)					41.7	50
(range)					(6-151)	(5-152)
Race(n,%)						
White	84(65)	80(62)	71(62)	66(59)	78(64)	70(60)
Black	29(22)	33(26)	28(24)	29(26)	28(23)	31(26)
Hispanic	16(12)	12(9)	15(13)	12(11)	15(12)	12(10)
Other	1(1)	4(3)	1(1)	4(4)	1 (1)	4(4)
Weight	36.8	41.1	36.1	41.1	36.5	40.55
(means,*lbs*)	(15-119)	(14-150)	(15-119)	(17-150)	(14.5-119)	(13.8-150)
(range)						
Number of Past AOM* Episodes						
(mean, *number*)	1.1	1.0	1.1	1.0	1.0	.95
(range)	(0-4)	(0-4)	(0-3)	(0-3)	(0-3)	(0-3)
Study Drug Duration						
(mean, *days*)	10.1	10.1			10.2	10.2
(range)	(4-14)	(2-13)			(4-17)	(4-19)

***AOM=acute otitis media**

*Medical Officer's Comments: **The demographic characteristics of the ITT and applicant and medical officer efficacy evaluable patients for both the TMP and TMP+SMX treatment regimen arms appear similar in gender distribution, race and weight. However, there is a trend towards decreased age for patients treated with TMP in both the ITT and efficacy***

evaluable patients. For the ITT patient population, a comparison of the mean age of patients treated with TMP with the mean age of patients treated with TMP+SMX yields a p-value of 0.08, and for the applicant and medical officer evaluable patient population, a comparison of the mean age of patients in the two treatment arms is associated with a p-value of 0.05. In terms of clinical characteristics (for all patient populations: ITT, applicant and medical officer efficacy evaluable), patients in both treatment regimens had a similar number of previous episodes of AOM prior to study enrollment, and received the same number of days of study drug therapy. Please note that when the medical officer reviewed patient records for documentation of study drug duration, it was at times difficult to discern the date that study drug was discontinued. The noted study drug days are the medical officer's best estimation of study drug duration. The medical officer noted 2 patients in the TMP regimen with apparent treatment for > 14 days, and one patient in the TMP+SMX regimen with apparent treatment for >14 days. It should also be noted that the applicant's analysis of study drug compliance in ITT patients revealed that a total of 104 (80%) TMP patients and 112 (87%) TMP+SMX patients were at least 80% compliant with the course of study medication.

Efficacy Analyses

Overall Clinical Response Evaluation

The following tables summarize the clinical outcome for the ITT, applicant and medical officer efficacy evaluable patients by treatment regimen:

ASSESSMENT OF OVERALL CLINICAL RESPONSE AT ENDPOINT* FOR INTENT TO TREAT PATIENT POPULATION

	Treatment Regimen	
	TMP	TMP+SMX
	n (%)	n (%)
Total Patients	130	129
Successful	94 (72.3)	94 (72.9)
Unsuccessful	36 (27.7)	35 (27.1)

***Visit 4 (Day 30) or last evaluation**

Medical Officer's Comments: A successful response was observed in 94 of 130 (72.3%) patients in the TMP regimen as compared to 94 of 129 patients in the TMP+SMX regimen. The 95% confidence interval around the true difference in the overall clinical success rates is as follows:

Clinical Success Rate (ITT Patient Population): [-12.2%, 11.0%]

ASSESSMENT OF OVERALL CLINICAL RESPONSE AT ENDPOINT* FOR EFFICACY EVALUABLE PATIENT POPULATION AS RENDERED BY APPLICANT

	Treatment Regimen	
	TMP	**TMP+SMX**
	n (%)	**n (%)**
Total Patients	115	111
Successful	82 (71.3)	78 (70.3)
Unsuccessful	33 (28.7)	33 (29.7)

** Visit 4 (Day 30)

Medical Officer's Comments: A successsful response was observed in 82 of 115 (71.3%) of applicant evaluable patients in the TMP regimen, as compared to 78 of 111 (70.3%) patients in the TMP+SMX regimen. The 95% confidence interval around the true difference in the overall clinical success rates is as follows:

Clinical Success Rate (Applicant Evaluable Patient Population): [-11.7%, 13.8%]

Two TMP patients, 24/018 and 24/024, were inadvertently included in the efficacy evaluable analysis by the applicant despite the use of systemic antimicrobials while enrolled in the trial. These patients are considered not evaluable in the medical officer's efficacy evaluation that follows. By the applicant's analysis, there appears to be no apparent age or gender-related patterns for the overall clinical response rates at endpoint for either the ITT or applicant efficacy evaluable patient populations.

ASSESSMENT OF OVERALL CLINICAL RESPONSE AT ENDPOINT* FOR EFFICACY EVALUABLE PATIENT POPULATION AS RENDERED BY MEDICAL OFFICER

	Treatment Regimen	
	TMP	**TMP+SMX**
	n (%)	**n (%)**
Total Patients	122	117
Successful	88 (72.1)	83 (70.9)
Unsuccessful	34 (27.9)	34 (29.1)

***Visit 4 or last evaluation**

Medical Officer's Comments: A successful response was observed in 88 of 122 (72.1%) medical officer evaluable patients in the TMP regimen as compared to 83 of 117 (70.9%)

patients in the TMP+SMX regimen. The 95% confidence interval around the true difference in the overall clinical success rates is as follows:

Clinical Success Rate (Medical Officer Evaluable Patient Population): [-11.3%, 13.3%]

Note: Using the Division of Anti-Infective Drug Product's (DAIDP) "two-tailed 95% confidence interval around the difference in outcomes" data analysis approach, the ITT and evaluable patient population confidence intervals should cross zero and remain within a lower bound delta of -20% to establish equivalence with the comparator regimen.

The confidence intervals for the ITT, applicant and medical officer evaluable patient analyses meet the DAIDP's requirements for demonstration of therapeutic eqivalence.

D. SAFETY EVALUATION
Protocol T-OM-02

Medical Officer's Comments: To assess the safety of trimethoprim in pediatric patients, the medical officer reviewed and analysed the safety database provided by the applicant for patients enrolled in Protocol T-OM-02. The information regarding the safety of patients studied under Protocol T-OM-02 has been taken from the applicant's submission, which has been reviewed by the statisticians at the Food and Drug Administration for appropriateness and accuracy. Tables used in the subsequent review of safety parameters which have been imported from the applicant's report/summary of this protocol will be identified throughout the discussion.

The following patient populations were included in the safety analyses:

All Safety Patients

All patients randomized into the study who received at least one dose of study drug.

Laboratory Safety Patients

All patients randomized into the study who received at least one dose of study drug and who had both initial and a follow-up laboratory assessments.

ALL SAFETY PATIENTS
Adverse Events

The following table, prepared by the applicant, summarizes the adverse events reported for patients by treatment regimen:

ADVERSE EVENTS BY TREATMENT REGIMEN
PROTOCOL T-OM-02

Adverse Event (AE) Category	Treatment Regimen: TMP n (%)	Treatment Regimen: TMP+SMX n (%)
Total Patients	133	129
Patients with at Least One AE	61 (45.8)	60 (46.5)
Patients with at Least One Severe AE	2 (1.5)	2 (1.6)
Patients in Whom Relationship of AE to Study Drug was Possible or Probable	11 (8.3)	27 (20.9)
Patients Who Discontinued from the Study Because of AE or Intercurrent Illness	4 (3.0)	3 (2.3)

Medical Officer's Comments: ***The incidence of adverse events was similar for patients in each treatment regimen [61/133 (45.9%) vs 60/129 (46.5%)]. The incidence of severe adverse events was similar for each treatment regimen [2/133 (1.5%) vs 2/129 (1.6%)].***

Note 1: ***Five severe events were reported in four patients [TMP patients 23/013 (pharyngitis) and 26/024 (left arm burn) and TMP+SMX patients 24/037 (skin rash) and 26/036 (pain reported twice)]. Only the skin rash in patient 24/037 was considered possibly related to study drug.***

Note 2: ***Serious adverse events were defined by the following accepted criteria:***
Any adverse event which:
--was fatal (even if it occurred more than 30 days post-treatment).
--was life-threatening or potentially life-threatening.
--resulted in permanent disability.
--required hospitalization or prolongation of hospitalization.
--involved cancer, a congenital anomaly, or the result of a drug overdose.
--suggested significant hazard to the patient.

One patient in the TMP treatment arm experienced a potentially serious event. Patient 42/007, an almost two year old male, was enrolled in the trial on 9/21/94 with bilateral otitis media, and H. influenzae susceptible to trimethoprim was cultured from the right middle ear aspirate. The child was examined by the investigator on 9/24/94 and 10/5/94 and was designated a partial and complete responder, respectively. The patient received his last dose of TMP on 10/1/94. At the final visit, on 10/22/94, he was found to have resolving pneumonia. The patient's provate physician had prescribed Biaxin on 10/17/94.

Additionally, the applicant reports a statistically significant difference (p=0.05) was shown in the incidence of treatment-related adverse events between TMP patients [11patients (8.3%)] and TMP+SMX patients [27 patients (20.9%)]. The applicant notes that this difference is most apparent in the incidence of skin rash occurring in TMP patients [1 event, (0.8%)] and TMP+SMX patients [10 events (7.8%)]. Please refer to Table S-23 below (prepared by the applicant) for a summary of treatment-related adverse events.

Table S-23
TREATMENT-RELATED ADVERSE EVENTS AS JUDGED BY INVESTIGATOR
All Safety Patients

	TMP	TMP+SMX	P Value
Number of Patients Enrolled	133 (100%)	129 (100%)	
Patients with at least one Adverse Event	11 (8.3%)	27 (20.9%)	0.005
Body as a whole			
abdominal pain	2 (1.5%)	5 (3.9%)	0.276
fever	1 (0.8%)	3 (2.3%)	
headache	1 (0.8%)	0	
	0	2 (1.6%)	
Digestive system			
anorexia	8 (6.0%)	12 (9.3%)	0.358
diarrhea	1 (0.8%)	2 (1.6%)	
flatulence	6 (4.5%)	7 (5.4%)	
vomiting	0	1 (0.8%)	
	3 (2.3%)	2 (1.6%)	
Nervous system			
insomnia	0	3 (2.3%)	0.118
screaming syndrome	0	2 (1.6%)	
	0	1 (0.8%)	
Skin			
rash	1 (0.8%)	10 (7.8%)	0.005
	1 (0.8%)	10 (7.8%)	

Note: A patient may appear more than once within a body system.

Two-tailed significance levels were computed using Fisher's Exact Test (SAS, PROC FREQ).

The adverse events were categorized according to the COSTART coding system.

Treatment-Related Events = Adverse events possibly or probably related to study drug as determined by investigator.

The incidence of adverse events or intercurrent illnesses leading to discontinuation were similar for the two treatment regimens. Such events leading to discontinuation were reported in 4 (3.0%) of the TMP patients: 23/013 (pharyngitis), 24/024 (streptococcal pharyngitis), 28/011 (sinus infection), and 29/010 (diarrhea, vomitng, and rash), and in 3 (2.3%) of the TMP+SMX patients: 23/010 (rash), 23/016 (allergic rash), and 27/010 (possible streptococcal

pharyngitis). None of the adverse events leading to discontinuation in the TMP group were study drug-related while two of the discontinuations in the TMP+SMX group were considered probably study drug-related, according to the investigator.

Adverse Events by Body System

Adverse events were reported and tabulated by body system and treatment regimen. Table S-17 (prepared by the applicant), compares the frequency of adverse events in study protocol patients:

Table S-17
ADVERSE EVENTS - ALL SAFETY PATIENTS
Frequency (Number of Adverse Events)

	TMP	TMP+SMX
Total Patients Enrolled	133	129
Total Adverse Events	98	99
Adverse Events by Body System		
Body as a whole	33	25
abdominal pain	5	5
allergic reaction	0	1
cyst	1	0
fever	7	1
flu-like syndrome	2	0
headache	2	2
infection	7	7
pain	9	9
Respiratory system	29	29
asthma	1	1
bronchitis	0	1
increased cough	8	10
laryngitis	1	1
lung disorder	2	2
pharyngitis	5	5
rhinitis	11	9
sinusitis	1	0
Digestive system	24	18
anorexia	2	2
constipation	3	0
diarrhea	10	9
flatulence	0	1
G.I. disorder	1	0
vomiting	8	6
Skin	8	13
eczema	2	0
herpes simplex	1	0
herpes zoster	1	0
rash	4	12
skin disorder	0	1

The adverse events were categorized according to the COSTART coding system.

Table S-17 (continued)
ADVERSE EVENTS - ALL SAFETY PATIENTS
Frequency (Number of Adverse Events)

	TMP	TMP+SMX
Nervous system	2	6
hyperkinesia	0	1
insomnia	1	4
nervousness	1	0
screaming syndrome	0	1
Special systems	1	4
conjunctivitis	1	3
ear disorder	0	1
Hemic and Lymphatic System	0	2
ecchymosis	0	1
lymphadenopathy	0	1
Cardiovascular system	1	0
migraine	1	0
Muscle system	0	2
bone fracture	0	2

The adverse events were categorized according to the COSTART coding system.

Medical Officer's Comments: ***The incidence of adverse events for the body as a whole, and by organ system (respiratory, digestive, skin, nervous, hemic and lymphatic, cardiovasular, and muscular and bone) are not statistically different for patients assigned to the two treatment regimens.***

Laboratory Assessments

Table 40 (prepared by the applicant) provides a summary of out-of-range laboratory values at baseline and at the last study visit for patients eligible for laboratory safety analysis, using an extended range of ≤20% below the normal range (low) or ≥20% above the normal range (high):

TABLE 40
Out-of-Range Laboratory Values at Baseline and End of Study – Laboratory Safety Patients
(Study No. T-OM-02)

Lab Test		BASELINE								
		TMP					TMP+SMX			
		N	Low		High		N	Low		High
Hematologic										
HEMOGLOBIN	(g/dL)	94	12	(12.8%)	0	(0.0%)	91	11	(12.1%)	0 (0.0%)
HEMATOCRIT	(%)	94	10	(10.6%)	0	(0.0%)	91	7	(7.7%)	0 (0.0%)
WBC	(x $10^3/mm^3$)	94	0	(0.0%)	20	(21.3%)	91	1	(1.1%)	13 (14.3%)
PLATELET COUNT	(x $10^3/mm^3$)	94	0	(0.0%)	1	(1.1%)	91	0	(0.0%)	3 (3.3%)
MCH	(pg)	94	0	(0.0%)	0	(0.0%)	91	2	(2.2%)	0 (0.0%)
MCV	(fL)	94	0	(0.0%)	0	(0.0%)	91	1	(1.1%)	0 (0.0%)
RBC	(x $10^6/mm^3$)	94	0	(0.0%)	0	(0.0%)	91	0	(0.0%)	0 (0.0%)
MCHC	(g/dL)	94	0	(0.0%)	0	(0.0%)	91	0	(0.0%)	0 (0.0%)
Hepatic										
SGOT	(IU/L)	88	0	(0.0%)	22	(25.0%)	89	0	(0.0%)	22 (24.7%)
SGPT	(IU/L)	91	4	(4.4%)	0	(0.0%)	92	1	(1.1%)	1 (1.1%)
BILIRUBIN TOTAL	(mg/dL)	90	0	(0.0%)	1	(1.1%)	88	0	(0.0%)	0 (0.0%)
Renal										
CREATININE	(mg/dL)	91	75	(82.4%)	0	(0.0%)	90	76	(84.4%)	0 (0.0%)
BUN, SERUM	(mg/dL)	93	5	(5.4%)	2	(1.1%)	94	3	(3.2%)	1 (1.1%)

Out of Range Laboratory Value:
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

TABLE 40 (cont'd)

END OF STUDY

Lab Test		TMP					TMP+SMX				
		N	Low		High		N	Low		High	
Hematologic											
HEMOGLOBIN	(g/dL)	91	11	(12.1%)	0	(0.0%)	86	12	(14.0%)	0	(0.0%)
HEMATOCRIT	(%)	91	11	(12.1%)	0	(0.0%)	86	7	(8.1%)	0	(0.0%)
WBC	(x $10^3/mm^3$)	91	1	(1.1%)	7	(7.7%)	86	1	(1.2%)	3	(3.5%)
PLATELET COUNT	(x $10^3/mm^3$)	91	0	(0.0%)	1	(1.1%)	86	1	(1.2%)	1	(1.2%)
MCH	(pg)	91	0	(0.0%)	0	(0.0%)	86	2	(2.3%)	0	(0.0%)
MCV	(fL)	91	0	(0.0%)	0	(0.0%)	86	1	(1.2%)	0	(0.0%)
RBC	(x $10^6/mm^3$)	91	0	(0.0%)	0	(0.0%)	86	0	(0.0%)	0	(0.0%)
MCHC	(g/dL)	91	0	(0.0%)	0	(0.0%)	86	0	(0.0%)	0	(0.0%)
Hepatic											
SGOT	(IU/L)	84	0	(0.0%)	21	(25.0%)	86	0	(0.0%)	9	(10.5%)
SGPT	(IU/L)	88	2	(2.3%)	0	(0.0%)	87	2	(2.3%)	0	(0.0%)
BILIRUBIN TOTAL	(mg/dL)	84	0	(0.0%)	1	(1.2%)	86	0	(0.0%)	0	(0.0%)
Renal											
CREATININE	(mg/dL)	86	70	(81.4%)	0	(0.0%)	87	70	(80.5%)	0	(0.0%)
BUN, SERUM	(mg/dL)	89	3	(3.4%)	1	(2.2%)	86	3	(3.5%)	1	(1.2%)

Out of Range Laboratory Value:
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

Medical Officer's Comments: A clinically significant change is apparent with regard to the total white blood cell count. At baseline, 20 (21.5%) patients in the TMP regimen and 13(14.3%) patients in the TMP+SMX regimen had higher than normal leukocyte counts. At the end of the study, the number of patients with high leucocyte counts dropped to 7 (7.7%) in the TMP regimen and to 3 (3.5%) in the TMP+SMX regimen.

Table 41 (prepared by the applicant) provides a summary of laboratory values that showed a shift in category (normal, low, or high) or remained unchanged from baseline to the last study visit for all hematology and biochemistry assessments:

TABLE 41
Laboratory Assessments: Comparison from Baseline to End of Study – Laboratory Safety Patients
(Study No. T-OM-02)

			No Change or Improved					Change Worse				
Lab Test	Treatment	Total N	LL	NN	HH	LN	HN	NL	NH	LH	HL	p-value
Complete Blood Count												
Hemoglobin (g/dL)	TMP	79	51	13	0	8	0	7	0	0	0	0.7657
	TMP+SMX	76	52	15	0	4	0	5	0	0	0	
Hematocrit (%)	TMP	79	58	8	0	5	0	8	0	0	0	0.7810
	TMP+SMX	76	56	10	0	4	0	6	0	0	0	
WBC ($x10^3/mm^3$)	TMP	79	2	37	12	0	23	2	3	0	0	0.3960
	TMP+SMX	76	2	45	5	0	16	6	2	0	0	
Platelet Count ($x10^3/mm^3$)	TMP	79	0	73	0	1	3	0	2	0	0	0.4364
	TMP+SMX	76	0	66	2	0	4	1	3	0	0	
MCH (pg)	TMP	79	32	35	0	6	0	6	0	0	0	1.0000
	TMP+SMX	76	32	33	1	4	0	6	0	0	0	
MCV (fL)	TMP	79	14	53	0	5	0	7	0	0	0	0.7657
	TMP+SMX	76	25	44	0	2	0	5	0	0	0	
RBC ($x10^6/mm^3$)	TMP	79	35	28	0	6	0	10	0	0	0	0.8166
	TMP+SMX	76	28	27	1	9	0	11	0	0	0	
MCHC (g/dL)	TMP	79	25	22	0	16	0	16	0	0	0	0.8403
	TMP+SMX	76	25	29	0	8	0	14	0	0	0	
Serum Chemistry												
SGPT (IU/L)	TMP	78	7	54	0	12	2	2	1	0	0	0.4949
	TMP+SMX	79	7	59	0	6	1	6	0	0	0	
SGOT (IU/L)	TMP	73	0	27	27	0	9	0	10	0	0	0.4446
	TMP+SMX	77	0	42	19	0	9	0	7	0	0	
BUN (mg/dL)	TMP	77	2	59	0	6	3	3	4	0	0	1.0000
	TMP+SMX	80	0	63	1	5	3	4	4	0	0	
Creatinine (mg/dL)	TMP	75	62	3	0	8	0	2	0	0	0	0.6175
	TMP+SMX	77	71	1	0	4	0	1	0	0	0	
Total Bilirubin (mg/dL)	TMP	74	0	72	0	0	1	0	1	0	0	0.4901
	TMP+SMX	77	0	75	0	0	2	0	0	0	0	

Note: p-value is from a Fishers Exact text comparing no change/improvement vs. Change worse.
N=within normal limits, L=Below normal limits, H=Above normal limits.

Medical Officer's Comments: ***No statistically significant shifts in category (normal,low,or high) were shown for any of the hematology or blood chemistry variables measured. A total of 23 patients in the TMP regimen and 16 patients in the TMP+SMX regimen, who had greater than normal white blood cell counts at entry, were found to have a white blood cell count in the normal range at the last study visit. These changes are what is to be expected in the recovery phase of an acute infection and these improvements were considered clinically significant.***

Table 42 (prepared by the applicant) provides a list of patients with laboratory assessments that shifted from normal values at baseline to values at post-treatment that were at least 20% above or below the normal range:

TABLE 42
Patients Whose Laboratory Assessments Were Normal at Baseline and Abnormal Post-Treatment Using the Extended Range - Laboratory Safety Patients
(Study No. T-OM-02)

Treatment Group	Site/ Patient	Laboratory Assessment	Normal Range	Baseline	Day 30	
TMP	22/003	PLATELET COUNT ($x10^3/mm^3$)	140.00 - 440.00	312.00	637.00	H
		SGPT (IU/L)	30.00 - 30.00	30.00	24.00	L
	22/005	LYMPHOCYTES (%)	20.00 - 40.00	36.00	72.00	H
		SEGMENTED NEUTR. (%)	50.00 - 70.00	56.00	23.00	L
	22/010	MONOCYTE (%)	1.00 - 6.00	1.00	8.00	H
		SGOT (IU/L)	15.00 - 37.00	33.00	45.00	H
	24/003	LYMPHOCYTES (%)	20.00 - 40.00	38.00	60.00	H
		SEGMENTED NEUTR. (%)	50.00 - 70.00	53.00	34.00	L
	24/013	CREATININE (mg/dL)	0.60 - 1.00	0.60	0.40	L
	24/018	LYMPHOCYTES (%)	20.00 - 40.00	29.00	60.00	H
		SEGMENTED NEUTR. (%)	50.00 - 70.00	68.00	39.00	L
	24/020	LYMPHOCYTES (%)	20.00 - 40.00	34.00	61.00	H
		SEGMENTED NEUTR. (%)	50.00 - 70.00	58.00	36.00	L
	24/038	EOSINOPHIL (%)	1.00 - 5.00	1.00	7.00	H
	24/043	LYMPHOCYTES (%)	20.00 - 40.00	26.00	56.00	H
		SEGMENTED NEUTR. (%)	50.00 - 70.00	70.00	39.00	L

* Change not clinically significant in the investigators opinion
** A letter from the investigator indicates that the patient had no clinical symptoms and a follow-up platelet count on 95APR14 was 376,000 per cubic millimeter.

Extended Range Laboratory Abnormality:
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

continued...

TABLE 42 (Cont'd)

Treatment Group	Site/ Patient	Laboratory Assessment		Normal Range	Baseline	Day 30	
TMP(cont.)	26/033	LYMPHOCYTES	(%)	20.00 - 40.00	26.00	58.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	68.00	36.00	L
		EOSINOPHIL	(%)	1.00 - 5.00	4.00	6.00	H
	27/007	LYMPHOCYTES	(%)	20.00 - 40.00	39.00	60.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	60.00	30.00	L
		MONOCYTE	(%)	1.00 - 6.00	1.00	9.00	H
	27/008	SEGMENTED NEUTR.	(%)	50.00 - 70.00	51.00	34.00	L
		SGOT	(IU/L)	15.00 - 37.00	34.00	57.00	H*
	27/016	MONOCYTE	(%)	1.00 - 6.00	2.00	9.00	H
	27/024	CREATININE	(mg/dL)	0.80 - 1.80	0.80	0.30	L
	27/036	WBC (x 10^3/mm^3)		4.80 - 10.80	9.80	15.60	H
		SGOT	(IU/L)	15.00 - 37.00	33.00	58.00	H*
	27/038	BUN, SERUM	(mg/dL)	7.00 - 18.00	15.00	28.00	H
	28/001	LYMPHOCYTES	(%)	20.00 - 40.00	40.00	56.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	57.00	40.00	L

* Change not clinically significant in the investigators opinion
** A letter from the investigator indicates that the patient had no clinical symptoms and a follow-up platelet count on 95APR14 was 376,000 per cubic millimeter.

Extended Range Laboratory Abnormality:
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

continued...

TABLE 42 (Cont'd)

Treatment Group	Site/ Patient	Laboratory Assessment		Normal Range	Baseline	Day 30	
TMP(cont.)	28/010	BILIRUBIN TOTAL	(mg/dL)	0.00 - 1.00	0.90	1.55	H*
	28/015	LYMPHOCYTES	(%)	20.00 - 40.00	28.00	48.00	H
	30/003	SGOT	(IU/L)	15.00 - 37.00	36.00	48.00	H
	30/005	SEGMENTED NEUTR.	(%)	50.00 - 70.00	51.00	35.00	L
	30/015	LYMPHOCYTES	(%)	20.00 - 40.00	24.00	49.00	H
	30/019	LYMPHOCYTES	(%)	20.00 - 40.00	38.00	69.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	62.00	28.00	L
	30/028	LYMPHOCYTES	(%)	20.00 - 40.00	39.00	58.00	H
	30/033	LYMPHOCYTES	(%)	20.00 - 40.00	39.00	64.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	59.00	36.00	L
	30/034	BUN, SERUM	(mg/dL)	7.00 - 18.00	10.00	4.00	L
	30/037	SEGMENTED NEUTR.	(%)	50.00 - 70.00	56.00	28.00	L
	30/048	WBC (x10^3/mm^3)		4.80 - 10.80	8.70	3.70	L
	30/049	SEGMENTED NEUTR.	(%)	50.00 - 70.00	69.00	30.00	L
		EOSINOPHIL	(%)	1.00 - 5.00	2.00	12.00	H

* Change not clinically significant in the investigators opinion
** A letter from the investigator indicates that the patient had no clinical symptoms and a follow-up platelet count on 95APR14 was 376,000 per cubic millimeter.

Extended Range Laboratory Abnormality:
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

continued...

TABLE 42 (Cont'd)

Treatment Group	Site/ Patient	Laboratory Assessment		Normal Range	Baseline	Day 30	
TMP(cont.)	30/057	EOSINOPHIL	(%)	1.00 - 5.00	3.00	9.00	H
TMP+SMX	22/004	LYMPHOCYTES	(%)	20.00 - 40.00	27.00	68.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	64.00	31.00	L
		WBC	($x10^3/mm^3$)	4.80 - 10.80	10.00	3.80	L
	23/010	SEGMENTED NEUTR.	(%)	50.00 - 70.00	52.00	24.00	L
		BUN, SERUM	(mg/dL)	7.00 - 18.00	9.00	5.00	L
	23/015	SEGMENTED NEUTR.	(%)	50.00 - 70.00	53.00	32.00	L
	24/006	EOSINOPHIL	(%)	1.00 - 5.00	4.00	6.00	H
	24/012	LYMPHOCYTES	(%)	20.00 - 40.00	34.00	48.00	H
	24/029	LYMPHOCYTES	(%)	20.00 - 40.00	30.00	48.00	H
	24/037	LYMPHOCYTES	(%)	20.00 - 40.00	21.00	69.00	H
	26/009	LYMPHOCYTES	(%)	20.00 - 40.00	30.00	64.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	64.00	31.00	L
	26/032	SEGMENTED NEUTR.	(%)	50.00 - 70.00	56.00	36.00	L
	27/013	LYMPHOCYTES	(%)	20.00 - 40.00	37.00	58.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	56.00	31.00	L
	27/023	LYMPHOCYTES	(%)	20.00 - 40.00	25.00	70.00	H

* Change not clinically significant in the investigators opinion
** A letter from the investigator indicates that the patient had no clinical symptoms and a follow-up platelet count on 95APR14 was 376,000 per cubic millimeter.

Extended Range Laboratory Abnormality:
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

continued...

TABLE 42 (Cont'd)

Treatment Group	Site/ Patient	Laboratory Assessment		Normal Range	Baseline	Day 30	
TMP+SMX(cont.)	27/025	SEGMENTED NEUTR.	(%)	50.00 - 70.00	54.00	24.00	L
		BUN, SERUM	(mg/dL)	7.00 - 18.00	14.00	23.00	H
	27/037	EOSINOPHIL	(%)	1.00 - 5.00	3.00	7.00	H
	27/043	LYMPHOCYTES	(%)	20.00 - 40.00	38.00	61.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	58.00	35.00	L
	28/002	LYMPHOCYTES	(%)	20.00 - 40.00	32.00	54.00	H
	28/004	LYMPHOCYTES	(%)	20.00 - 40.00	40.00	50.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	54.00	36.00	L
		EOSINOPHIL	(%)	1.00 - 5.00	4.00	12.00	H
	28/006	LYMPHOCYTES	(%)	20.00 - 40.00	27.00	55.00	H
	29/004	LYMPHOCYTES	(%)	20.00 - 40.00	35.00	58.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	57.00	37.00	L
	30/006	SEGMENTED NEUTR.	(%)	50.00 - 70.00	53.00	38.00	L
	30/007	LYMPHOCYTES	(%)	20.00 - 40.00	31.00	76.00	H
		SEGMENTED NEUTR.	(%)	50.00 - 70.00	60.00	21.00	L

* Change not clinically significant in the investigators opinion
** A letter from the investigator indicates that the patient had no clinical symptoms and a follow-up platelet count on 95APR14 was 376,000 per cubic millimeter.

Extended Range Laboratory Abnormality:
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

continued...

TABLE 42 (Cont'd)

Treatment Group	Site/ Patient	Laboratory Assessment		Normal Range	Baseline	Day 30	
TMP+SMX(cont.)	30/013	SGOT	(IU/L)	15.00 - 37.00	19.00	46.00	H
		SGPT	(IU/L)	30.00 - 65.00	33.00	9.00	L
	30/025	SEGMENTED NEUTR.	(%)	50.00 - 70.00	58.00	40.00	L
	30/026	EOSINOPHIL	(%)	1.00 - 5.00	3.00	6.00	H
	30/036	LYMPHOCYTES	(%)	20.00 - 40.00	23.00	72.00	H
	30/040	BUN, SERUM	(mg/dL)	7.00 - 18.00	7.00	4.00	L
	30/044	PLATELET COUNT	($x10^3/mm^3$)	140.00 - 440.00	269.00	83.00	L**
	30/052	EOSINOPHIL	(%)	1.00 - 5.00	5.00	10.00	H

* Change not clinically significant in the investigators opinion
** A letter from the investigator indicates that the patient had no clinical symptoms and a follow-up platelet count on 95APR14 was 376,000 per cubic millimeter.

Extended Range Laboratory Abnormality:
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

Medical Officer's Comments: Most of these changes were considered clinically insignificant by the medical monitor or participating investigator. Lymphocytes increased and segmented neutrophils decreased over time for patients in both treatment regimens, as might be expected during the recovery phase from an infection such as acute otitis media.

Discussions of the patients with laboratory abnormalities from both treatment regimens which could be considered clinically significant are listed by laboratory test below:

SGOT

TABLE 43

Patients With Normal SGOT Values at Baseline and at least 20% Above the Normal Range at the End of the Study - Laboratory Safety Patients
(Study No. T-OM-02)

Treatment Group	Site/ Patient	Age/Sex	SGOT (IU/L)		
			Normal Range	Baseline	End of Study
TMP	22/010	3yr/ male	15-37 IU/L	33	45
	27/008	3 yr/ male		34	57
	27/036	1 yr 9 mo/male		33	58
	30/003	1 yr 4 mo/male		36	48
TMP+SMX	30/013	7 mo/male		19	46

Source: Table 42

Medical Officer's Comments: In four patients in the TMP regimen, and one patient in the TMP+SMX regimen, SGOT values increased to at least 20% above the normal range. The applicant reports that all the noted changes were considered clinically insignificant by the investigators.

TOTAL BILIRUBIN

Medical Officer's Comments: One patient in the TMP regimen had a total bilirubin which increased from 0.09 mg/dL at baseline to 1.55 mg/dL at the last study yisit. The patient's parent refused further laboratory test to monitor this abnormality. The investigator concluded that the child possible had Gilbert's Syndrome, and that the elevated bilirubin was not related to study drug.

PLATELET COUNT

Medical Officer's Comments: One patient in the TMP+SMX regimen, had a platelet count of 269 X 10^3/mm at baseline and 83 X 10^3/mm at the last study visit. The investigator stated that a repeat platelet count performed 9 months after the study ended, was normal (376 X 10^3/mm), and there was no evidence of a hematologic disorder or abnormal bleeding tendency.

Medical Officer's Final Comments on Safety Analyses for Protocol T-OM-02:

The incidence of at least one adverse event and at least one severe adverse event are similar for both treatment regimens. The number of patients discontinued from the study because of adverse events or intercurrent illness are also similar for patient in the TMP and TMP+SMX treatment regimens. The incidence of adverse events for the body as a whole, and by organ system (respiratory, digestive, skin, nervous, hemic and lymphatic, cardiovasular, and muscular and bone) are not statistically different for patients assigned to the two treatment regimens. Additionally, the applicant reports a statistically significant difference (p=0.05) was shown in the incidence of treatment-related adverse events between TMP patients [11patients (8.3%)] and TMP+SMX patients [27 patients (20.9%)]. The applicant notes that this difference is most apparent in the incidence of skin rash occurring in TMP patients [1 event, (0.8%)] and TMP+SMX patients [10 events (7.8%)].

E. DISCUSSION/CONCLUSIONS

The Medical Officer recommends that Primsol Oral Solution (trimethoprim) be approved for the treatment of acute otitis media in pediatric patients. The results of the clinical efficacy study and safety analyses are supportive of the efficacy and safety of trimethoprim in pediatric patients ≥ 6 months of age. The clincal efficacy analysis satisfies the DAIDP's requirements for demonstrating therapeutic equivalence to another agent approved for the treatment of acute otitis media, trimethoprim plus sulfamethoxazole. More specific labeling guidance will be predicated on the results of the bacterial efficacy analysis performed in Protocol T-OM-01 (to follow).

II. REVIEW OF CLINICAL STUDIES (Continued)
INDICATION: ACUTE OTITIS MEDIA
Protocol: T-OM-01

Title: Open Trial of Primsol Solution (Trimethoprim) Utilizing Tympanocentesis in Pediatric Patients with Acute Otitis Media.

Study Dates: February 9, 1994-August 23, 1995.

Objective: To evaluate the clinical and bacteriologic efficacy and safety of Primsol solution (trimethoprim) in the treatment of acute otitis media in pediatric patients.

A. STUDY SUMMARY

Study Design: Open-label, multidose, multicenter study in pediatric patients diagnosed with acute otitis media utilizing tympanocentesis to evaluate the bacteriologic efficacy of trimethoprim solution.

Method of Patient Assignment: All patients who met the stated inclusion and exclusion criteria for the study and whose parents signed a consent form for their child's participation in the study were assigned a patient number in sequential order and enrolled in the study. This was an open-label study and all patients received Primsol Solution.

Inclusion Criteria:

Patients meeting the following criteria were included in the study protocol:

1. age range: 6 months to 12 years.
2. Males or females.
3. Outpatients (not hospitalized).
4. ***Diagnosis of acute otitis media*** was made as follows:
   - by the presence of one or more of the following clinical symptoms: pain in the affected ear, lethargy, irritability, or fever.
   - by examination of the tympanic membrane and the presence of one or more of the following signs: dilation of the blood vessels on the malleus and at the annulus, diffuse dullness, erythema, loss of normal landmarks, bulging of the drum.
   - by evidence of middle ear effusion in the affected ear documented by pneumatic otoscopy and/or tympanometry.
5. **Baseline tympanocentesis: Baseline tympanocentesis and culture of middle ear fluid.**

Exclusion Criteria:

Patients meeting any of the following criteria were to be excluded from study entry:

1. History of allergy to trimethoprim.
2. Chronic otitis media (5 or more episodes, including the current episode, in the past 12 months).
3. Suppurative otitis media.
4. Concurrent use of antihistamines or decongestants.
5. Known clinical history or signs (in the judgement of the clinical investigator) of significant renal impairment (>50% elevation above the upper limit of normal in serum creatinine values), hepatic dysfunction (>50% increase above the upper limit of normal in serum ALT,AST,and/or bilirubin), or patients with hematologic abnormality or cardiovascular disease requiring medical intervention.
6. Patients with a history of glucose-6-phosphate dehydrogenase deficiency, folate deficiency, or megaloblastic anemia.
7. Patients with known or suspected severe allergies or bronchial asthma.
8. Treatment with other antimicrobials within 14 days prior to entry or during this study.
9. History of neutropenia or opportunistic infections.
10. Malabsorption syndrome.
11. Anticonvulsant therapy with phenytoin.
12. Presence or evidence of another significant underlying disease which precludes evaluation of response to therapy, including states of immunosuppression.
13. Patients with craniofacial defects.
14. Previous otic surgery.
15. Treatment with another investigational drug within 30 days prior to study entry or during this study.
16. Positive urine pregnancy test in females of childbearing potential.
17. Parents/Guardians of patients unable or unwilling to sign informed consent form.

Study Drug, Dosage, and Duration of Therapy:

The recommeded dose of Primsol Solution (25 mg trimethoprim/5 mL) was 10 mg/kg/day (maximum dosage=400 mg per day), given in two divided doses every 12 hours for 10 days. The timing of dosing in relation to meals was not considered important to the design of the trial, or the absorption of the antimicrobial.

Concomitant Therapy:

All medications taken within 30 days prior to entry to the study were recorded. All medications that were continued during the study period were recorded on the CRF. Antihistamines, decongestants, and other antimicrobial agents were not to be administered during the study period. Antipyretic agents were to be administered at the discretion of the parent/guardian or physician.

Schedule of Assessments:

The following figure provides a study flow chart showing timing of visits and measurements recorded at each visit during the protocol:

FIGURE 1
Flow Chart of Study
(Study No. T-OM-01)

	Visit 1	Visit 2	Visit 3	Visit 4[a]
	Day 1 (Screen)	Day 4	Day 15	Day 30
Inclusion/Exclusion Criteria	X			
Medical History	X			
Physical Examination	X	(brief)	(brief)	(brief)
Assess Acute Otitis Media Symptoms	X	X	X	X
Assess Acute Otitis Media Signs	X	X	X	X
Assess Patient Response (CR, PR, NR, Relapse, Recurrence)		X	X	X
Tympanocentesis & Middle Ear Effusion Culture	X	X[b]	X[b]	X[b]
Assess Adverse Experience(s)		X	X	X
Concomitant Medication	X	X	X	X
Serum Chemistry	X			X
Complete Blood Count	X			X
Drug Accountability	X	X	X	

Source: Appendix 1, Protocol
[a] If a patient was withdrawn from the study prior to Visit 4, all these procedures were performed.
[b] Only if warranted.
CR=complete response; PR=partial response; NR=no response

Schedule of Assessments:

Clinical Assessments:

Clinical Evaluations, Visits 1-4: At each visit, a physical examination was performed, including pneumatic otoscopy and/or tympanometry to assess signs and symproms of acute otitis media. All important characteristics of the tympanic membranes including color, transparency, luster, mobility, and vascularity were evaluated. Presence or absence of middle ear effusion was documented.

Clinical Response: See EVALUABILITY CRITERIA AND EFFICACY EVALUATIONS Section to follow.

Microbiologic Assessments:

Middle Ear Fluid (Aspirate) Culture and Susceptibility Testing:

Baseline tympanocentesis was required for all patients prior to initiating therapy with Primsol Solution to perform bacteriologic culture and sensitivity testing. Both ears were aspirated if the patient had bilateral acute otitis media. A repeat aspiration and culture of the middle ear fluid was recommended if patients demonstrated clinical failure, relapse, or recurrence and had not received any antimicrobial therapy other than the study drug. Bacterial isolates were identified using standard methods. The status of B-lactamase production was to be determined for all *H. influenzae* and *M. catarrhalis* isolates. Antimicrobial susceptibility of bacterial isolates to trimethoprim was determined in accordance with the National Committee for Clinical Laboratory Standards by *in vitro* disc diffusion.

Since NCCLS has not published zone diameter interpretive standards for trimethoprim alone against *S. pneumoniae*, *H. influenzae* or M. catarrhalis, a decision was made to follow the NCCLS guidelines published for the combination product , trimethoprim plus sulfamethoxazole. Empirically, zone diameter standards for *S. pneumoniae* were chosen to be the same as those recommended for *H. influenzae*. Please see table below:

	Disc Content
Trimethoprim	5 mcg
Trimethoprim/sulfamethoxazole	1.25/23.75 mcg

	Zone Diameter, mm		
	Resistant	Intermediate	Susceptible
S. pneumoniae	≤10	11-15	≥16
H. influenzae	≤10	11-15	≥16
M. catarrhalis	≤10	11-15	≥16

Microbiologic Response: See EVALUABILITY CRITERIA AND EFFICACY EVALUATIONS Section to follow.

Safety Assessments (Adverse Events and Laboratory Evaluation):

Adverse Events: Parents/Guardians were instructed to report any adverse events to the investigator. At each clinical assessment, all new or continuing adverse events, as well as worsening baseline conditions, were recorded, regardless of severity and relationship to study drug. All serious or unexpected adverse events were to be reported immediately by telephone to Oxford Research International Corporation and to the applicant, and a written report was required to be submitted to the medical monitor within 24 hours. All serious adverse events were to be followed through resolution.

Laboratory Evaluation: Laboratory tests. including complete blood counts, and serum chemistries including serum creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin, and blood urea nitrogen were to be obtained at the initial and last follow-up visits, or more often if considered medically indicated by the clinical investigator.

B. EVALUABILITY CRITERIA AND EFFICACY EVALUATIONS

Applicant Criteria for Evaluable Patients:

The following patient populations were included in the safety analyses:

Intent-To-Treat Patients

All patients with the exception of the three patients with no follow-up visits after baseline visit.

Efficacy Patients

The following patient populations were included in the the clinical and bacteriologic efficacy analyses:

Clinical Efficacy Evaluable Patients

1. No chronic otitis media, as defined in the protocol.
2. Patient received study drug > 7 days (unless the patient was discontinued prior to this due to insufficient relief or an adverse event).
3. Patient received no concomitant systemic antihistamine or decongestant for 3 or more consecutive days.
4. Patient received no other antimicrobial therapy before Visit 4 (day 30), unless given for treatment failure for acute otitis media.
5. Day 30 visit >22 days (unless unsuccessful response or discontinued for treatment-related adverse event).

6. No antimicrobial therapy taken within 14 days prior to entry (as per protocol).
7. No other major protocol violation.

Bacteriologic Efficacy Evaluable Patients

1. A causative pathogen was isolated at Visit 1.
2. The bacterial isolate was susceptible to trimethoprim.
3. Patient received no other antimicrobial therapy before Study Day 15, unless for treatment failure for acute otitis media.
4. Clinical evaluation was conducted at Visit2 (Day 4) and Visit 3 (Day 15).
5. Patient received doses for > 7 days (unless the patient was discontinued prior to this due to insufficient relief or an adverse event).

Medical Officer's Comments: The medical officer agrees with the evaluability criteria for clinical and bacteriologic efficacy.

Applicant Assessment of Clinical Response:

The investigator made an assessment of patient **Clinical Response** to treatment on days 4, 15 and 30 (Visits 2, 3, and 4, respectively) according to the following criteria:

Visit 2 Evaluation (Day 4):

Complete Response: Complete resolution of baseline signs and symptoms with or without middle ear effusion. No new significant signs or symptoms of acute otitis media.

Partial Response: Partial resolution of baseline signs and symptoms with or without middle ear effusion. No new significant signs or symptoms of acute otitis media.

No Response: No resolution of baseline signs and symptoms. Appearance of significant new signs and symptoms of acute otitis media.

Visit 3 Evaluation (Day 15):

Complete Response: See Visit 2 definition.

Partial Response: See Visit 2 definition.

Relapse: Complete Response or Partial Response at Visit 2. Reappearance or increase of significant signs and symptoms of acute otitis media.

Visit 4 Evaluation (Day 30):

Complete Response: See Visit 2 definition.

Partial Response: See Visit 2 definition.

Recurrence: Reappearance of significant signs and symptoms of acute otitis media at Visit 4 (Day 30), after demonstration of a Complete Response at Visit 3.

The applicant analysed **Overall Clinical Response** at Visit 3 and Visit 4 as follows:

Early Cure: Complete Response on Visit 2 (Day 4), Complete Response at Visit 3 (Day 15), no Relapse, no Recurrence.

Late Cure: Partial Response at Visit 2, Complete Response at Visit 3, no Relapse, no Recurrence.

Improvement: Partial Response at Visit 2 or Visit 3, with no Relapse, no Recurrence.

Failure: No Response at Visit 2.

Relapse: Complete Response or Partial Response at Visit 2 with reappearance or increase in significant signs and symptoms at Visit 3.

Recurrence: Complete Response at Visit 3 with reappearance of significant signs and symptoms of acute otitis media at Visit 4.

Medical Officer's Comments: Note: ***In the Intent-To-Treat Analysis, those patients missing Visit 4 evaluation and showing only improvement through Visit 3 were considered failures. Patients with an early or late cure missing the Visit 4 evaluation were considered cures in the Intent-To-Treat analysis.***

The applicant also made an assessment of **Overall Clinical Response at Endpoint** as

successful (Early Cure, Late Cure, or Improvement)
or
unsuccessful (Failure, Relapse, or Recurrence) at endpoint (last evaluation).

Applicant Assessment of Bacteriologic Response:

Baseline tympanocentesis and culture of middle ear fluids/effusions were required for all patients prior to initiating therapy with Primsol Solution. Repeat aspiration and culture of middle ear fluid was recommended if there was evidence of clinical failure on Visit 2. Repeat aspiration and

culture were also recommended if patients demonstrated relapse or recurrence.

Since a second tympanocentesis could not be recommended for children who were cured or improved, a culture-based analysis of bacteriologic response was not possible.

Presumed bacteriologic eradication was defined as cases in which baseline aspirate cultures were positive for a causative pathogen and patients showed a Complete or Partial Response at Visit 2 with no Relapse on Visit 3 (Day 15).

Presumed bacteriologic persistence was defined as a positive culture of the middle ear aspirate at baseline and with clinical Failure at Visit 2 or with clinical Relapse at Visit 3 (Day 15).

*Medical Officer's Comments: **The Medical Officer agreed with the applicant's assessment for clinical response in clinical efficacy evaluable patients. For bacteriologic efficacy evaluable patients, the medical officer performed an additional analysis by taking the Overall Clinical Response at Visit 4 into account (i.e. the applicant's analysis only takes the clinical response at Visit 3 into account; therefore, patients evaluated as recurrences on Visit 4 would not be evaluated as clinical failures or presumed bacteriologic persistence in the applicant's analysis).***

C. STUDY DESIGN, PATIENT EVALUATION, AND EFFICACY ANALYSES

Study Design and Evaluability

The applicant conducted this study protocol with patients enrolled by investigators at 7 centers in the United States. Overall, 120 patients were enrolled.

The next table summarizes the number and distribution of patients enrolled by center:

NUMBER OF PATIENTS ENROLLED BY CENTER
Protocol T-OM-01

Investigator/Center Number	Number of Patients Enrolled
McCarty/40	47
Deabate/41	2
Reisinger/42	7
Feris/44	21
Stoltz/45	10
Aldrich/46	8
Thint/47	25
Total Patients	120

Medical Officer's Comments: Although one center (40) enrolled a substantial proportion of the total patients (39%), no center enrolled greater than 50% of the ITT patient population.

The following table summarizes the numer of patients in the Intent-To-Treat (ITT), clinical efficacy evaluable and not evaluable, and bacteriologic efficacy evaluable and not evaluable patient populations as rendered by the applicant:

INTENT TO TREAT (ITT) AND EVALUABLE AND NOT EVALUABLE PATIENTS PER APPLICANT

No. of **ITT Patients**	120*
No. of **Clinical Efficacy Evaluable Patients**	102
No. of Clinical Efficacy Not Evaluable Patients	18
No. of **Bacteriologic Efficacy Evaluable Patients**	58
No. of Bacteriologic Efficacy Not Evaluable Patients	62

* Three patients were lost to follow-up after enrollment in the study, and therefore have no post-baseline information available. The applicant did not include these patients in the Intent-To-Treat analysis.

Medical Officer's Comments: The medical officer has reviewed the clinical and bacteriologic evaluations by visit for each of the 120 enrolled patients. Overall, the medical officer agrees with the applicant's evaluation and reporting of the clinical and bacteriologic efficacy for the determined evaluable patients. Therefore, the medical officer will use and discuss the applicant's evaluation and analysis of the clinical and bacteriologic efficacy evaluable patient populations. The medical officer will add an additional analysis based upon overall clinical response at Visit 4 for the bateriologic efficacy evaluable patient population when the applicant's evaluation of this patient population is discussed.

Note: The medical officer did find that for a number of middle ear isolates--particularly for the coagulase-negative staphylococcus isolates--susceptibility data were not recorded in the appropriate tables, although the patients with these isolates were considered to be a part of the bacteriologic efficacy evaluable patient population. The medical officer has assumed that these tests were performed, particularly since coagulase-negative staphylococci are not considered primary pathogens in the etiology of acute otitis media, and allowed the applicant to include these patients in the bacteriologic efficacy analysis.

Patient Enrollment by Investigation Site

The following table summarizes the number and distribution of patients in the Intent-To-Treat,

and clincial and bacteriologic efficacy evaluable patient populations by investigation site as rendered by the applicant:

INTENT TO TREAT (ITT) AND EVALUABLE PATIENTS BY INVESTIGATION SITE (AS RENDERED BY THE APPLICANT)

	EVALUABLE PATIENT POPULATIONS		
Investigator/Center Number	ITT	Clinical Efficacy	Bacteriologic Efficacy
McCarty/40	47	41	18
Deabate/41	2	2	1
Reisinger/42	7	6	4
Feris/44	21	21	13
Stoltz/45	10	9	5
Aldrich/46	8	8	6
Thint/47	25	15	11
Total Patients	120 (117)*	102	58

* Three patients were lost to follow-up after baseline exam and visit, and were not included in the Intent-To-Treat analysis performed by the applicant.

Medical Officer's Comments: No center enrolled greater than 50% of the ITT or efficacy evaluable population.

Demographic and Clinical Characteristics of Intent-To-Treat and Efficacy Evaluable Patients

The demographic and clinical characteristics of the Intent-To-Treat, clinical, and bacteriologic efficacy evaluable patient population (as rendered by the applicant) are presented as follows:

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF INTENT-TO-TREAT, CLINICAL, AND BACTERIOLOGIC EFFICACY EVALAUBLE PATIENTS (AS RENDERED BY APPLICANT)

Characteristic	ITT n=117	CLINEVAL** n=102	BACTEVAL*** n=58
Age			
(mean,*years*,range)	2.5 (0.5-12.0)	2.6 (0.5-12.0)	2.8 (0.5-12.0)
Sex			
Male	70 (60%)	62 (61%)	34 (59%)
Female	47 (40%)	40 (39%)	24 (41%)
Race			
Caucasian	53 (45%)	47 (46%)	30 (52%)
Hispanic	43 (37%)	41 (40%)	22 (38%)
Black	19 (16%)	12 (12%)	6 (10%)
Asian	1 (1%)	1 (1%)	0
Other	1 (1%)	1 (1%)	0
Weight			
(mean, *lbs*,range)	32.5 (15.0-124.0)	33.3 (15.0-124.0)	33.7 (15.0-124.0)
No. of Previous AOM* Episodes in Past 12 month			
(mean, *number*, range)	1.1 (0-4)	0.9 (0-3)	1.0 (0-4)

***AOM= Acute Otitis Media**
****CLINEVAL=Clinical Efficacy Evaluable Patients**
*****BACTEVAL=Bacteriologic Efficacy Evaluable Patients**

Medical Officer's Comments: The demographic characteristics of the ITT and clinical and bacteriologic efficacy evaluable patients appear similar in age, gender distribution, weight, and race. It should also be noted that the mean duration of therapy for the Intent-To-Treat patients was 10.2 days, and the applicant reported that a total of 87 (75%) patients in the Intent -To-Treat patient population were at least 80% compliant.

Efficacy Analyses

Clinical Efficacy Evaluation

Intent to Treat and Clinical Efficacy Patient Population Evaluation

One hundred and two patients of 117 total Intent-To-Treat patients were found evaluable for clinical efficacy by the applicant.

The next tables summarize the applicant's reasons for excluding patients from the clinical efficacy analyses:

SUMMARY OF APPLICANT REASONS FOR EXCLUSION FROM CLINICAL EFFICACY ANALYSIS

Reason for Exclusion from Clinical Efficacy Analysis	Number of Patients
Dosed less than 7 days	2
Chronic Otitis Media	4
Visit 4 (Day 30) missing	9
Total	15

The following table presents the overall clinical response at endpoint for the ITT and clinical efficacy evaluable patient populations (as rendered by the applicant):

OVERALL CLINICAL RESPONSE AT ENDPOINT* FOR THE INTENT TO TREAT AND CLINICAL EFFICACY EVALUABLE PATIENT POPULATION (AS RENDERED BY APPLICANT)

Overall Clinical Response	ITT (%) n=117	CLINICAL EFFICACY (%) n=102
Successful Response	**78 (66.7%)**	**72 (70.6%)**
Early Cure	13 (11%)	12 (11.8%)
Late Cure	41 (35%)	38 (37.3%)
Improvement	24 (20.5%)	22 (21.6%)
Unsuccessful Response	**39 (33.3%)**	**30 (29.4%)**
Failure	18 (15.4%)	10 (9.8%)
Relapse	13 (11.1%)	13 (12.7%)
Recurrence	8 (6.8%)	7 (6.9%)

***Visit 4 or last evaluation**

***Medical Officer's Comments:** As shown in the table, for the ITT patient population, a Successful Response (Early Cure, Late Cure, and Improvement) was observed in 78 of 117 (66.7%) patients and 39 (33.3%) were evaluated as having an Unsuccessful Response (Failure, Relapse, or Recurrence).*

Bacteriologic Efficacy Evaluation

Bacteriologic Efficacy Patient Population Evaluation

Fifty-eight patients with susceptible pathogens were found to be evaluable for bacteriologic efficacy by the applicant.

The next tables summarize the applicant's reasons for excluding patients from the bacteriologic efficacy analyses:

SUMMARY OF APPLICANT REASONS FOR EXCLUSION FROM BACTERIOLOGIC EFFICACY ANALYSIS

Reason for Exclusion from Bacteriologic Efficacy Analysis	Number of Patients
No Baseline Pathogen	38
Pathogen Resistant to Study Drug	18
No Clinical Assessment at Visit 3	6
Total	62

Middle Ear Isolates: Primary Pathogens and Susceptibility Testing

All 120 patients enrolled in the study underwent tympanocentesis in an attempt to isolate a primary pathogen (*S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*) from middle ear effusion. In some patients the procedure was performed in both ears. At least one primary pathogen was recovered from 54 patients. The middle ear aspirates from 66 patients had either no growth or grew bacterial species other than the three primary pathogens. Of the 54 patients with primary pathogen isolates, 7 patients grew more than one primary pathogen. Thus, a total of 66 primary pathogens were obtained from 54 patients. The next table presents primary pathogen susceptibility testing for TMP:

PRIMARY PATHOGENS SUSCEPTIBILITY TESTING FOR TRIMETHOPRIM

Pathogen	Isolates (number)	Susceptible Isolates	Resistant Isolates	Test Not Performed
S. pneumoniae	34	28 (82%)	4 (12%)	2 (6%)
H. influenzae	27	20*(74%)	7 (26%)	0
M. catarrhalis	5	0	5 (100%)	0
Total	66	48 (73%)	16 (24%)	2 (3%)

* One isolate (H. influenzae), susceptible to trimethoprim/sulfamethoxazole, not tested against TMP alone.

Medical Officer's Comments: Of the 34 S. pneumoniae isolates cultured, 28 (82%) isolates were susceptible to trimethoprim. Twenty of 27 (74%) H. influenzae isolates were susceptible to trimethoprim. It should be noted that none of the 5 M. catarrhalis isolates were susceptible to trimethoprim.

Bacteriologic Response in Bacteriologic Efficacy Evaluable Patients

The next table presents a summary of Bacteriologic Response to TMP at Visit 3 for each susceptible pathogen isolated at baseline:

ASSESSMENT OF BACTERIOLOGIC RESPONSE TO TRIMETHOPRIM IN BACTERIOLOGIC EFFICACY EVALUABLE PATIENTS AT VISIT 3

Pathogen	Patients (number)	Presumed Eradication		Presumed Persistence	
		Cured N (%)	Improved N (%)	Failed N (%)	Relapsed N (%)
Primary Pathogens*					
S. Pneumoniae	20	12 (60)	4 (20)	2 (10)	2 (10)
H. Influenzae	17	10 (59)	4 (23)	2 (12)	1 (6)
B-lactamase+	6	3 (50)	2 (33)	1 (17)	0
B-lactamase-	9	7 (78)	0	1 (11)	1 (11)
ND	2	0	2 (100)	0	0
Total	37	22 (59.5)	8 (21.6)	4 (10.8)	3 (8.1)
Other Pathogens**					
S. epidermidis	10	7 (70)	2 (20)	1 (10)	0 (0)
Staphylococcus species	11	8 (72.7)	2 (18.2)	1 (9.1)	0 (0)
Total	21	15 (71.4)	4 (19)	2 (9.5)	0 (0)

*** All pathogens susceptible to trimethoprim. One isolate (H. influenzae), susceptible to trimethoprim plus sulfamethoxazole, not tested against trimethoprim alone.**

**** Pathogens susceptible to trimethoprim or susceptibility unknown.**

Medical Officer's Comments: Thirty-seven of the 58 bacteriologic efficacy evaluable patients had primary pathogens. Of the 37 patients with primary pathogens, 30 (81.1%) had a presumed bacterial eradication and 7 (18.9%) had a presumed bacterial persistence.

Twenty-one patients had "other" pathogens: 10 had S. epidermidis isolates and 11 had staphylococcal species. Nine of the 10 (90%) patients with S. epidermidis had presumed

bacterial eradication as did 10 of 11 (91%) patients with staphylococcal species.

It should be noted that 4 patients had 2 primary pathogens (S. pneumoniae and H. influenzae), and they were included in the H. influenzae tabulations only. Likewise 2 patients with both H. influenzae and S. aureus were evaluated only for H. influenzae.

The applicant presented the following table as the 95% confidence interval limits around the proportion of presumed eradications by pathogen after Visit 3 (i.e. not including recurrences at Visit 4):

Pathogen	*% Eradication*	*Confidence Interval (Limit)*
S. pneumoniae	*80.0*	*(55.7, 93.4)*
H. influenzae	*82.4*	*(55.8, 95.4)*
Total, Primary Pathogens	*81.1*	*(64.3, 91.5)*
Total, Other Pathogens	*90.5*	*(68.2, 98.4)*

The medical officer performed an additional analysis of bacteriologic efficacy at Visit 4. This analysis included patients who were determined by the applicant to be clinical successes and presumed bacterial eradications at Visit 3, but were determined to be recurrences at Visit 4. The medical officer found three patients with recurrences of AOM at Visit 4, who were considered evaluable, and had no tympanocentesis to document new or superinfection. Two of these patients (40/012 and 45/08) had S. pneumoniae isolated from MEE at baseline. One patient (40/40) had H. influenzae isolated from MEE at baseline. Thus, an analysis of the proportion of presumed eradication by pathogen after Visit 4 yields:

Pathogen	*% Eradication*
S. pneumoniae	*70.0*
H. influenzae	*76.5*
Total, Primary Pathogens	*73.0*

D. SAFETY EVALUATION
Protocol T-OM-01

Medical Officer's Comments: To assess the safety of trimethoprim in pediatric patients, the medical officer reviewed and analysed the safety database provided by the applicant for patients enrolled in Protocol T-OM-01. The information regarding the safety of patients studied under Protocol T-OM-01 has been taken from the applicant's submission, which has been reviewed by the statisticians at the Food and Drug Administration for appropriateness and accuracy. Tables used in the subsequent review of safety parameters which have been imported from the applicant's report/summary of this protocol wil be identified throughout the discussion.

The following patient populations were included in the safety analyses:

All Safety Patients

All patients enrolled into the study who received at lease one dose of study drug.

Laboratory Safety Patients

All patients enrolled into the study who received at least one dose of study drug and who had both initial and follow-up laboratory assessments.

ALL SAFETY PATIENTS
Adverse Events

The following table, prepared by the applicant, summarizes the adverse events reported for patients in Protocol T-OM-01:

Adverse Event (AE) Category	N	%
Total Patients Receiving Trimethoprim	120	
Patients with at Least One AE	36	30.0
Patients with at Least One Severe AE	1	0.8
Patients in Whom Relationship of AE to Study Drug as Possible or Probable	8	6.7
Patients Who Discontinued from the Study Because of AE or Intercurrent Illness	3	2.5

Medical Officer's Comments: Thirty-six (30%) of 120 patients treated with trimethoprim had at least one adverse event. One severe adverse event (stomach flu) was reported in one patient. Serious events were defined by the following accepted criteria:
Any adverse event which:
--was fatal (even if it occurred more than 30 days post-treatment).
--was life-threatening or potentially life-threatening.
--resulted in permanent disability
--required hospitalization or prolongation of hospitalization.
--involved cancer, a congenital anomaly, or the result of a drug overdose.
--suggested significant hazard to the patients.

One serious adverse event was reported during the study. The serious event (meningitis requiring hospitalization) was reported in a 2 year old male, who had completed his visits for otitis media. This patient had been hospitalized for bacterial meningitis approximately two weeks prior to enrollment in the study protocol. At the last study visit, the patient was found to have a recurrence of his bacterial meningitis. He was hospitalized, treated with intravenous chloramphenicol and ampicillin, and reported to have made and uneventful recovery.

Adverse events judged by the investigator to be treatment-related were reported in 8 (6.7%) patients. Adverse events or intercurrent illnesses leading to discontinuation were reported in 3 (2.5%) patients: 40/025 (bronchitis), 40/028 (impetigo), and 40/036 (skin rash). None of these adverse evnets were evaluated to be related to study drug. The incidence of at least one adverse event, as well as the incidence of severe adverse events are similar to those seen for patients treated with the trimethoprim regimen in Protocol T-OM-02. Further, the percentage of patients whose adverse events appeared related to study drug, or were discontinued from the study because of an adverse event or intercurrent illness were similar for patients treated with trimethoprim in Protocol T-OM-01 and T-OM-02. Of the 120 patients receiving TMP in Protocol T-OM-01, 8 patients (6.7%) reported a total of 10 adverse events which were possibly or probably study drug-related. This proportion of patients is similar to the number of patients in Protocol T-OM-02 reported with treatment-related adverse events (8.3%). Table 36 (prepared by the applicant) summarizes by body system all reported treatment-related adverse events as judged by the investigator:

TABLE 36

Treatment-Related Adverse Events Judged by Investigator – All Safety Patients
(Study No. T-OM-01)

	TMP
Number of Patients Enrolled	120
Patients with at least one Treatment-Related Adverse Event	8 (6.7%)
Digestive system	
diarrhea	7 (5.8%)
dyspepsia	5 (4.2%)
nausea	1 (0.8%)
saliva increased	1 (0.8%)
	1 (0.8%)
Nervous system	
nervousness	1 (0.8%)
	1 (0.8%)
Skin	
rash	1 (0.8%)
	1 (0.8%)

Note: A patient may appear more than once.

The adverse events were categorized according to the COSTART coding system.

Treatment Related Events = Adverse events possibly or probably related to study drug as determined by investigator.

Adverse Events by Body System

Adverse events were reported and tabulated by body system. Table 32 (prepared by the applicant), summarizes the frequency of adverse events in trimethoprim-treated patients by body system:

TABLE 32
Analysis of Adverse Events: All Events – All Safety Patients
(Study No. T-OM-01)

	TMP
Number of Patients Enrolled	120 (100%)
Patients with at least one Adverse Event	36 (30.0%)
Body as a whole	10 (8.3%)
flu like syndrome	2 (1.7%)
headache	3 (2.5%)
infection	5 (4.2%)
Digestive system	11 (9.2%)
diarrhea	8 (6.7%)
dyspepsia	1 (0.8%)
nausea	2 (1.7%)
saliva increased	1 (0.8%)
vomiting	3 (2.5%)
Hemic and Lymphatic System	1 (0.8%)
anemia	1 (0.8%)
Nervous system	2 (1.7%)
meningitis	1 (0.8%)
nervousness	1 (0.8%)
Respiratory system	12 (10.0%)
asthma	1 (0.8%)
bronchitis	2 (1.7%)
increased cough	5 (4.2%)
pharyngitis	1 (0.8%)
pneumonia	1 (0.8%)
rhinitis	5 (4.2%)
sinusitis	1 (0.8%)
Skin	6 (5.0%)
herpes zoster	1 (0.8%)
pustular rash	1 (0.8%)
rash	4 (3.3%)
Special systems	4 (3.3%)
ear disorder	1 (0.8%)
otitis externa	1 (0.8%)
partial transitory deafness	1 (0.8%)
scleritis	1 (0.8%)

Note: A patient may appear more than once.
The adverse events were categorized according to the COSTART coding system.
ALL EVENTS = All adverse events without regard to study drug relationship.

Medical Officer's Comments: The incidence of adverse events for the body as a whole, and by organ system are the same or lowere than those reported for trimethoprim-treated patients in Protocol T-OM-02.

Laboratory Assessments

Table 45 (prepared by the applicant) provides a summary of out-of-range laboratory values at baseline and last study visit for patients eligible for laboratory safety analysis, using an extended range of ≤20% below the normal range (low) or ≥20% above the normal range (high).

TABLE 45
Out-of-Range Laboratory Values at Baseline and Day 30 – Laboratory Safety Patients
(Study No. T-OM-01)

Baseline

Lab Test		TMP				
		N	Low		High	
Hematologic						
HEMOGLOBIN	(g/dL)	107	12	(11.2%)	0	(0.0%)
HEMATOCRIT	(%)	107	9	(8.4%)	0	(0.0%)
WBC	(x 10**3)	107	1	(0.9%)	44	(41.1%)
MCH	(pg)	107	2	(1.9%)	0	(0.0%)
MCV	(fL)	107	3	(2.8%)	0	(0.0%)
RBC	(x 10**6/mm3)	107	2	(1.9%)	0	(0.0%)
MCHC	(g/dL)	107	1	(0.9%)	0	(0.0%)
PLATELET COUNT	(1000/mm3)	105	0	(0.0%)	17	(16.2%)
Hepatic						
SGOT	(IU/L)	104	1	(1.0%)	18	(17.3%)
SGPT	(IU/L)	105	2	(1.9%)	6	(5.7%)
BILIRUBIN TOTAL	(mg/dL)	105	1	(1.0%)	1	(1.0%)
Renal						
CREATININE	(mg/dL)	105	65	(61.9%)	0	(0.0%)
BUN, SERUM	(mg/dL)	107	5	(4.7%)	2	(1.9%)

Out of Range Laboratory Value.
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

continued...

Table 45 (cont'd)

Day 30

Lab Test		TMP				
		N	Low		High	
Hematologic						
HEMOGLOBIN	(g/dL)	86	7	(8.1%)	0	(0.0%)
HEMATOCRIT	(%)	86	5	(5.8%)	0	(0.0%)
WBC	(x 10**3)	86	2	(2.3%)	20	(23.3%)
MCH	(pg)	86	5	(5.8%)	0	(0.0%)
MCV	(fL)	86	4	(4.7%)	0	(0.0%)
RBC	(x 10**6/mm3)	86	0	(0.0%)	0	(0.0%)
MCHC	(g/dL)	86	0	(0.0%)	0	(0.0%)
PLATELET COUNT	(1000/mm3)	86	1	(1.2%)	11	(12.8%)
Hepatic						
SGOT	(IU/L)	82	0	(0.0%)	14	(17.1%)
SGPT	(IU/L)	82	2	(2.4%)	2	(2.4%)
BILIRUBIN TOTAL	(mg/dL)	83	0	(0.0%)	0	(0.0%)
Renal						
CREATININE	(mg/dL)	84	55	(65.5%)	0	(0.0%)
BUN, SERUM	(mg/dL)	84	4	(4.8%)	2	(2.4%)

Out of Range Laboratory Value.
Low = Laboratory assessment 20% or more below the normal range.
High = Laboratory assessment 20% or more above the normal range.

Medical Officer's Comments: ***A clinically significant change is apparent with regard to the total white blood cell count. At baseline, 44 patients (41.1%) had higher than normal leukocyte counts. At the end of the study, the number of patients with a high leukocyte count dropped to 20 (23.3%). These changes are what is to be expected in the recovery phase of an acute infection.***

Table 46 (prepared by the applicant) provides a summary of laboratory values that showed a shift in category (normal, low, or high) or remained unchanged from baseline to the last study visit for all hematology and biochemistry assessments:

TABLE 46

Laboratory Assessments: Change in Category from Baseline to Day 30 - Laboratory Safety Patients (Study No. T-OM-01)

Lab Test	TMP Group									
	Total N	LL	LN	LH	NL	NN	NH	HL	HN	HH
Hematologic										
HEMOGLOBIN	77	35	7	0	10	22	1	0	2	0
HEMATOCRIT	77	42	4	0	12	17	0	0	2	0
WBC	77	1	2	0	2	24	5	2	17	24
MCH	77	38	2	0	5	32	0	0	0	0
MCV	77	32	4	0	3	36	0	0	0	2
RBC	77	20	9	0	6	41	0	0	1	0
MCHC	77	21	7	0	10	39	0	0	0	0
PLATELET COUNT	76	0	0	0	0	49	9	0	10	8
Hepatic										
SGOT	73	0	1	0	0	36	6	0	11	19
SGPT	73	3	5	0	5	47	4	0	4	5
BILIRUBIN TOTAL	74	0	0	0	0	72	0	0	2	0
Renal										
CREATININE	75	53	0	0	3	19	0	0	0	0
BUN, SERUM	75	1	7	0	3	60	2	0	1	1

L = Low = Laboratory assessment below the normal range.
N = Normal = Laboratory assessment within the normal range.
H = High = Laboratory assessment above the normal range.
For the headings LL, LN,..., the first letter denotes the pre-treatment result, the second letter denotes the post-treatment result.

Medical Officer's Comments: No clinically or statistically significant shifts in category were noted by the applicant for any of the laboratory parameters studied in trimethoprim-treated patients in Protocol T-OM-01.

Medical Officer's Final Comments on Safety Analyses for Protocol T-OM-01: No additional safety concerns are raised by review of the database of Protocol T-OM-01.

E. DISCUSSION/CONCLUSIONS

Medical Officer's Comments and Recommendations for the Indication of Acute Otitis Media in Pediatric Patients:

The DAIDP's "Points To Consider" document and the publication "Guidelines for the Evaluation of Anti-infective Drug Products" in the Clinical Infectious Diseases journal in 1992, recommend two clinical trials to establish the effectiveness of an antimicrobial product in treating the infection of acute otitis media: one statistically adequate and well-controlled multicenter trial documenting comparable clinical efficacy with an antimicrobial agent approved for treatment of acute otitis media, and a second study utilizing tympanocentiesis to document microbiologic efficacy. Protocol T-OM-02 fulfills the requirement for one statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product.

Protocol T-OM-01 was designed to fulfill the requirement for a second trial, as an open study utilizing baseline tympanocentesis to establish microbiologic etiology and efficacy. The "Points to Consider " document recommends that this study should establish acceptable microbial and clinical outcome in at least 25 patients with H. influenzae, in at least 25 patients with S. pneumoniae, and in at least 15 patients with M. catarrhalis. It should be noted that the initial goal of this protocol was to enroll at least 60 bacteriologically evaluable patients with the following infections: 25 patients with S. pneumoniae, 20 patients with H. influenzae, and 15 patients with M. catarrhalis, and that it was believed that the enrollment of 100 patients would yield at least 60 bacteriologically evaluable patients with the above expected distribution. Unfortunately, difficulty was encountered in recruiting patients for the otitis media tympanocentesis study, and it became apparent during the trial that the goal to isolate the pre-determined number of specific organisms from middle ear fluid aspirates would not be met--even when enrollment was extended to 120 patients. The applicant states that in a meeting held between the FDA and Ascent personnel on April 19, 1995, the FDA agreed to allow Ascent to file the tympanocentesis trial results with fewer than the pre-determined number of specific isolated organisms.

The medical officer's review of Protocol T-OM-01 reveals that the microbiologic efficacy data from this clinical trial cannot fulfill the requirements for the specified number of patients infected with the three major bacterial pathogens associated with acute otitis media. The number of pathogens studied, and the presumed bacterial eradication rates for the two

primary pathogen, S. pneumoniae and H. influenzae support granting the acute otitis media indication for these two pathogens. However, only 5 M. catarrhalis organisms were isolated, and none were susceptible to trimethoprim.

The "Points to Consider" document offers the following guidance for labeling in this type of situation:

"Pathogens listed in the final product label should be those of the three listed above that had acceptable eradication rates. If a product failed to have acceptable clinical and microbiologic effectiveness against all three microorganisms, the product should be listed only for those microorganism(s) that it eradicated. It should also receive a "restricted" listing as "not a product for first line therapy". This restriction should be based on the empiric nature of the treatment of this disease at the present time, and the need for true first-line therapies to be efficacious against all of the presently common bacterial pathogens associated with this infection. To receive an unrestricted label in this infection, the investigative product should be compared to a product with an unrestricted label in the "clinical only trial" outlined previously in this section."

The Medical Officer recommends that trimethoprim be approved for the treatment of acute otitis media caused by S. pneumoniae and H. influenzae in pediatric patients ≥ 6 months of age at a dose of 10 mg per kg per day (maximum 400 mg per day) given in divided doses every twelve hours for ten days. As recommended by the "Points to Consider" document, this should be a restricted listing, as "not a product for first line therapy".

II. REVIEW OF CLINICAL STUDIES (Continued)

A. STUDY SUMMARY

III. SUMMARY RECOMMENDATIONS AND LABELING GUIDANCE

The medical officer recommends that Primsol Oral Solution (Trimethoprim) be approved for the treatment of acute otitis media due to susceptible strains of Streptococcus pneumoniae and Haemophilus influenzae in pediatric patients from 6 months to 12 years of age at a dose of 10 mg per kg per day (up to a maximum of 400 mg per day), administered in two divided doses every 12 hours by mouth. This indication should be a "restricted" listing as "not a product for first line theapy". Dosage and administration guidelines for treatment of acute otitis media in pediatric patients can be listed under a separate section in the Dosage and Administration Section of the label, and providing a table as a guideline for attainment of this dosage based on patient weight can be considered for inclusion (labeled specifically for pediatric patients 6 months of age or older).

A separate section for Pediatric Patients could also be created in the Adverse Reactions Section of the label to discuss the occurrence and incidence of adverse events reported in the pediatric clinical trials reviewed, with particular attention to adverse events reported in pediatric patients, and not currently listed in the Adverse Reactions Section (e.g., laboratory abnormalities such as increased eosinophils and lymphocytes).

The Microbiology Section of the label should be updated to include data such as the minimum drug concentration inhibiting microbial growth (MIC) and MIC interpretive standards for causative pathogens in acute otitis media—i.e., S. pneumoniae and H. influenzae.

This concludes the review of NDA/ANDA 74-374, Clinical Efficacy Supplement for Pediatric Patients.

MD

Susan A. Maloney, M.D., M.H.S.
Reviewing Medical Officer
Division of Anti-Infective Drug Products

cc: Original NDA 74-374
HFD-340
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/MO/SMaloney
HFD-520/Pharm/
HFD-520/Micro/HSilver
HFD-520/Chem/MKochnar
HFD-520/Stat/RHarkins
HFD-520/CSO/CDeBellas
HFD-520/CSO/BDuval-Miller

Concurrence Only:
HFD-520/DivDir/DFeige 12.20.96
HFD-520/SMO/JSoreth 12/19/96